5368-1

# THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF THE NATIONAL TUBERCULOSIS ASSOCIATION

## ABSTRACTS OF TUBERCULOSIS

EDITOR
ALLEN K. KRAUSE, Baltimore, Maryland

ASSOCIATE EDITOR
MAX PINNER, Ithaca, N. Y.

EDITORIAL STAFF

E. R. BALDWIN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
ESMOND R. LONG, Philadelphia, Pa.
J. A. MYERS, Minneapolis, Minn.

VOLUME XXXVII
JANUARY-JUNE, 1938

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

# THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

EDITOR
ALLEN K. KRAUSE, Baltimore, Maryland

ASSOCIATE EDITOR
MAX PINNER, Ithaca, N. Y.

EDITORIAL STAFF

E. R. BALDWIN, Saranac Lake, N. Y.
H. J. CORPER, Denver, Col.
ESMOND R. LONG, Philadelphia, Pa.
J. A. MYERS, Minneapolis, Minn.

VOLUME XXXVII
JANUARY-JUNE, 1938

10879

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

## CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JANUARY, 1938


**Notes on the Choice of Roentgenological Diagnostic Methods.** CHARLES WEYL, S. REID WARREN, JR. AND DALLETT B. O'NEILL. 1

**Auxiliary Techniques in Chest Roentgenography.** CLARENCE J. ZINTHEO, JR. 14

**Roentgenographic Features of Tuberculosis in Bones and Joints.** CHARLES G. SUTHERLAND AND ERCELL A. ADDINGTON. 31

**Hernia of the Lung.** EPHRAIM KOROL. 39

**The Relative Value of Fluoroscopic, Roentgenographic and Physical Examinations in a Tuberculosis Case-Finding Program in University Students.** RUTH E. BOYNTON, HAROLD S. DIEHL AND CHARLES E. SHEPARD. 49

**The Degree of Tuberculosis in New Cases.** P. K. TELFORD. 57

**The Psychotherapy of Rehabilitation of Patients in Tuberculosis Hospitals.** CLARENCE M. HINCKS. 61

**Prognosis of the Cavity Bearer.** HERMAN SCHWATT AND ARTHUR REST. 65

**Tuberculous Mediastinitis.** R. H. KAMPMEIER. 71

**Intrapleural Fibrin Bodies.** SAMUEL A. ROBINS AND MARK H. JORESS. 81

**Haemorrhage in Pulmonary Tuberculosis.** CHARLES K. MCCARTHY. 88

**The Course of Experimental Pneumococcus Infection in Tuberculous Rabbits.** J. WEISSFEILER, E. N. MOROZOVA AND A. I. STRUKOV. 93

**Obituary—Henry Robert Murray Landis, 1872–1937.** 100

**Books.** 104


NUMBER 2, FEBRUARY, 1938


**Present Trend of Case Fatality Rates in Tuberculosis.** GODIAS J. DROLET. 125

**Selective Thoracoplasty with Lung Mobilization.** RICHARD H. OVERHOLT. 152

**Roentgenological Group Examinations for Pulmonary Tuberculosis.** ROBERT G. BLOCH, BYRON F. FRANCIS, C. WESLEY EISELE AND ELWOOD W. MASON. 174

**The Weltmann Serum Coagulation Reaction.** S. A. LEVINSON AND R. I. KLEIN. 200

**Intracutaneous Reactions against Antiserum in Tuberculosis.** H. J. CORPER AND C. B. VIDAL. 238

**Experimental Oleothorax.** D. H. Saley, H. S. Willis and Lucia Ellwart ..... 245
**Editorial—Has Tuberculosis Treatment Been Effective?** ..... 254

Number 3, March, 1938

**Statistical Basis of Errors in Immunity Tests.** William N. Berg .. 259
**Daily Variations in the Tuberculin Reaction. 1. The Range of Variation in Tuberculous and Control Subjects.** John S. Howe .. 264
**Daily Variations in the Tuberculin Reaction. 2. Relation to the Vascular Pressor Episode.** John S. Howe ..... 273
**The Possibility of Sensitization to Tuberculin.** Waldo E. Nelson, A. Graeme Mitchell and Estelle W. Brown ..... 286
**The Intracutaneous Tuberculin Reaction Associated with Calcified Intrathoracic Lesions.** Waldo E. Nelson, A. Graeme Mitchell and Estelle W. Brown ..... 311
**The Diagnosis and Treatment of Tuberculous Tracheobronchitis.** Wadsworth Warren, Arthur E. Hammond and William M. Tuttle ..... 315
**Bronchial Factor in Cavitation.** Sidney J. Shipman ..... 336
**The Progressive Primary Complex.** Oscar Auerbach ..... 346
**Generalized Nodular Tuberculosis.** J. E. Welker and Lee H. Leger ..... 354
**Obituary—Lawrason Brown, 1871–1937** ..... 361

Number 4, April, 1938

**A Functional Test in Chronic Pulmonary Disease.** Benjamin H. Schlomovitz, A. B. Thompson and L. Grant Glickman ..... 369
**Tuberculosis of the Gums and Cheeks.** George G. Martin and Sheldon W. Koepf ..... 381
**Thrombosis of Pulmonary Artery.** Jaime F. Pou and Robert Charr ..... 394
**Tuberculosis of Cervical Lymph Nodes.** Brian C. Thompson .... 410
**Bilateral Phrenic-Nerve Interruption in the Treatment of Pulmonary Tuberculosis.** Robert V. Cohen and George Willauer .... 420
**Sex Differences in Tuberculosis Mortality in the United States.** C. C. Dauer ..... 435
**The Influence of Sunlight upon Experimental Tuberculosis.** A. C. Ukil and S. R. Guha Thakurtha ..... 448

Number 5, May, 1938

**The Incidence of Extrapulmonary Primary Tuberculosis.** Henry C. Sweany and William L. M. Martinsen ..... 465

**Studies on the Retrogressive Changes of Tubercles.** HENRY C. SWEANY, ALMA E. TILLOTSON AND VINCENT KOZIELEK..... 484
**Tuberculous Dissemination during Therapeutic Pneumothorax.** WILLIAM A. ZAVOD..... 494
**Tuberculous Bacillaemia in Rabbits. 1. Bacillaemia in Nonallergic Animals.** JACQUES P. DUCHAINE..... 507
**Tuberculous Bacillaemia in Rabbits. 2. Bacillaemia in Allergic Animals.** JACQUES P. DUCHAINE..... 520
**The Flotation Method of Sputum Examination.** C. RICHARD SMITH. 525
**The Clinical versus the Public Health Point of View in the Treatment of Tuberculosis.** F. M. POTTENGER..... 533
**Positive Intrapleural Pressure as an Aid to Pneumothorax Therapy.** GEOFFREY EDSALL..... 542
**Tuberculous Infection in Negro Colleges.** PAUL B. CORNELY AND E. H. ALLEN..... 549
**A Study of the Results of Treatment of Pulmonary Tuberculosis in Mexican and White Patients.** FRED R. HARPER..... 556
**A Tuberculosis Survey in Jamaica.** E. W. FLAHIFF..... 560

NUMBER 6, JUNE, 1938

**Studies in Avian Tuberculosis.** A. B. CRAWFORD:
1. **Avian Tubercle Bacilli in Generalized Disease in Swine**..... 579
2. **Comparative Virulence of Avian and Bovine Tubercle Bacilli for Rabbits and Guinea Pigs**..... 582
3. **Sensitization Method of Differentiating Avian from Bovine Infection in Guinea Pigs and Rabbits**..... 588
4. **The Possible Rôle of the Avian Tubercle Bacillus in Infection in Man**..... 594

**The Effect of Human Tissue Juices on Tubercle Bacilli.** NELL HIRSCHBERG AND LLOYD ARNOLD..... 598
**Tuberculosis Control.** ROBERT E. PLUNKETT..... 612
**Tuberculous Infection in Kingston, Jamaica.** C. W. WELLS AND H. H. SMITH..... 625
**Fluoroscopy during Pneumothorax Treatment.** LOUIS COHEN AND JOHN V. BLADY..... 634
**The Effect of Age on the Total Pulmonary Capacity and Its Subdivisions.** NOLAN L. KALTREIDER, W. W. FRAY AND H. VAN ZILE HYDE..... 662
**Noncaseating Tuberculosis.** MAX PINNER..... 690

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

# NOTES ON THE CHOICE OF ROENTGENOLOGICAL DIAGNOSTIC METHODS[1]

CHARLES WEYL, S. REID WARREN, JR. AND DALLETT B. O'NEILL

## INTRODUCTION

Several methods for the diagnosis of tuberculosis and pneumonoconiosis require the use of X-rays. Of these methods the following are the most important:

(*1*) Stereoscopic posteroanterior, single posteroanterior, oblique and lateral roentgenograms on films made with full-wave rectified roentgen ray apparatus with exposures of 0.1 second or less
(*2*) Posteroanterior roentgenograms on films made with portable self-rectified apparatus, usually requiring exposure times from 0.25 second to 1.0 second
(*3*) Posteroanterior roentgenograms on paper
(*4*) Fluoroscopic examination

These general methods may of course be further subdivided. For example, there are several ways of choosing the factors involved in the first method so that roentgenograms of different density, contrast and sharpness are produced. It is the purpose of this paper to discuss certain advantages and disadvantages of each of these general methods. The detailed criteria for choosing the technical factors for each method have been described elsewhere (1, 2, 3).

In view of the increasing use of X-rays for the diagnosis of tuberculosis among school children and of pneumonoconiosis among industrial workers the choice of methods for such surveys becomes increasingly important. This paper is concerned chiefly with the problem of roentgen ray surveys.

## COMPARISON OF COST AND PRACTICABILITY

The approximate cost of apparatus and materials for the methods mentioned above is listed in table 1. These estimates include only the cost of apparatus and materials.

[1] This investigation was conducted at the Moore School X-ray Laboratory, University of Pennsylvania, under a grant from the National Tuberculosis Association.

There follows a brief description of some of the practical features of the methods listed in table 1.

Four-valve roentgenographic apparatus, with suitable auxiliary materials, is the most expensive and the heaviest of the several types listed. It is possible to construct a four-valve machine so that it may be transported by truck to a school or other building in which a number of patients are to be examined. The transportation and setting up of the equipment require two men and they in turn will need some assistance in unloading and loading the machine. These two men can make single posteroanterior roentgenograms at the rate of at least 25 films per hour. If proper precautions have been taken in the design of the apparatus and technique these roentgenograms are uniform and of high diagnostic quality.[2] If it is desired, stereoscopic pairs may be made, although this requires additional heavy equipment and of course more

TABLE 1

| DIAGNOSTIC METHOD | APPROXIMATE FIRST COST OF X-RAY EQUIPMENT | APPROXIMATE UNIT COST OF FILM OR PAPER AND PROCESSING CHEMICALS |
|---|---|---|
| Four-valve, 200 milliampere roentgenographic apparatus | $3,500.00 | $0.60 per roentgenogram (film)<br>$0.30 per roentgenogram (paper) |
| Portable 10 milliampere to 30 milliampere roentgenographic apparatus | $1,500.00 | $0.60 per roentgenogram (film)<br>$0.30 per roentgenogram (paper) |
| Fluoroscope | $1,200.00 | No materials |

time. After the films are exposed they must be taken to a darkroom in which they may be processed under accurately controlled conditions by a time-temperature method of development. Note that roentgenograms made in this manner satisfy high technical standards of contrast, sharpness and comparability.

Four-valve apparatus or mechanically rectified apparatus used with paper, cut to 14 by 17 inch size, requires the same procedure as that described in the last paragraph. If the paper is made in rolls[3] the processes of making the films and of processing them require less time. About 120 films per hour may be made by this method. The cost of each finished roentgenogram is approximately seventy-five cents.

[2] Apparatus of this type is used by the Pennsylvania Department of Health, the Georgia Department of Public Health and by Precision Radiographs, Inc.

[3] This method is used by the Powers X-ray Products, Inc.

Portable roentgenographic apparatus of modern design is light in weight and completely shockproof. It can be set up easily by one man in a few minutes and it does not, in general, require a large power supply line. However, the roentgenograms obtained with this apparatus either on film or on paper are excessively unsharp due to motion of the heart and other thoracic contents. With this apparatus also well controlled methods of development are required after the exposures have been made. If is difficult, however, to design this type of equipment in such a manner that the completed roentgenograms are comparable and of high diagnostic quality.

The fluoroscope is easily portable and the physician who interprets can act as operator. In all of the other methods described above an interpreter examines the films after they are processed, whereas in the case of the fluoroscope the interpretation is made during the examination.

## COMPARISON OF DIAGNOSTIC METHODS FROM THE TECHNICAL POINT OF VIEW

The cost and practicability of the several methods are not, of course, the most important factors from the diagnostic point of view. In this section the technical aspects are reviewed briefly.

Four-valve roentgenographic apparatus with suitable auxiliary materials can be adjusted to produce roentgenograms of the chest on X-ray film at focal spot-film distances from four feet to six feet and with exposure times of 0.1 second or less, which have densities within the diagnostic area from 0.4 to 1.5. If these films are examined by means of diffuse light of proper intensity the average observer's eye will perceive density differences within the diagnostic area of the order of 0.05.[4]

This perception of small density differences forms the basis of the X-ray diagnosis of diseases of the chest. That method which produces contrasts which are most easily perceived for a given type of lesion is the best method from the diagnostic point of view. In addition, however, it is necessary to produce sharp shadow borders if the diagnosis is to be accurately performed. This requires a small X-ray tube focal spot and a short exposure time, as well as high contrast. By the proper choice

[4] The technical factors here involved are very complicated. This statement may be used as a guide, but it is the authors' opinion that a precise determination of perceived contrast in roentgenograms requires extensive research. The quantitative statements presented in this section therefore represent a synthesis of available experimental data by the authors and other physicists with whom they have consulted. For example, see BRONKHORST, WILLEM: *Kontrast und Schärfe im Roentgenbilde*, Georg Thieme, Leipzig, 1927.

of apparatus and technique the unsharpness of the shadow of a part of the lung 15 cm. from the film may be as low as 0.4 mm., using four-valve roentgenographic apparatus with a stationary anode tube and X-ray film. This unsharpness varies depending on the phase of the cardiac cycle during which the exposure is made and upon the distance of the object from the film, as well as upon the other factors mentioned above.

If roentgenographic paper is used instead of film as the recording material, it must be viewed by reflected light. It is well known by photographers that it is impossible to perceive as small differences in density on paper as on film. This is, of course, due in part to the differ-

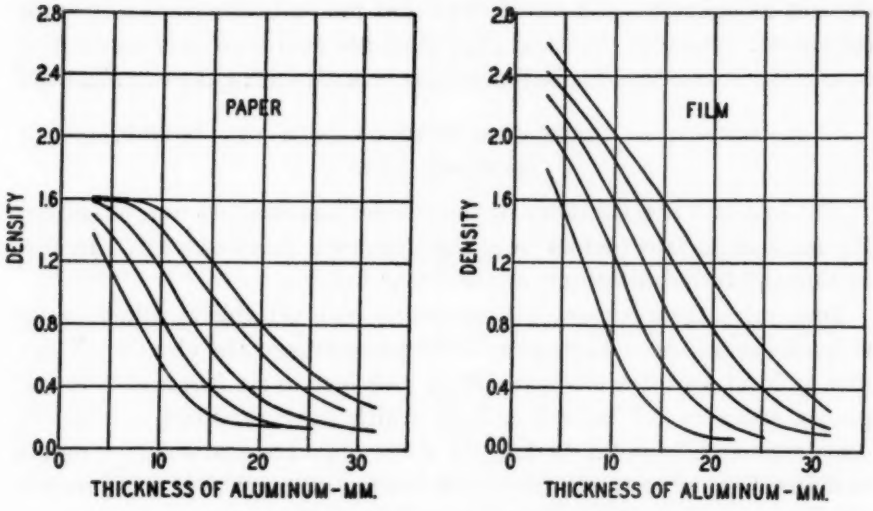



FIG. 1. Explanation in text; see table 2

ence in response of paper and of film to light or to X-rays, and in part to the viewing conditions. Films are viewed by means of transmitted light; paper roentgenograms are viewed by reflected light. The following tests were made to compare the observed densities and contrasts for paper and for film. Roentgenograms of an aluminum ladder were made on paper and on film at a focal spot-film distance of four feet, an exposure time of 0.1 second, an X-ray tube current of 100 milliamperes and X-ray tube voltages of 55 kvp., 60 kvp., 65 kvp., 70 kvp. and 75 kvp., with intensifying screens. The density of each ladder step of these roentgenograms was measured by means of a densitometer. The

data are shown in the curves on figure 1. It will be noted that (*1*) the average density for each roentgenogram on film is considerably higher than the average density on paper; (*2*) the average contrast on film is far greater than the average contrast on paper; (*3*) the upper limit of density for paper is approximately 1.6, whereas the upper limit of density for film rises continually and reaches in the case of the 75 kvp. roentgenogram a value of 2.6. These data are perhaps more clearly summarized in table 2.

TABLE 2

*Density and contrast of paper and of film for exposures made at 100 ma., 0.1 second, focal spot-film distance 4 feet, under 12.7 mm. of aluminum, and X-ray tube voltages of 55 kvp., 60 kvp., 65 kvp., 70 kvp. and 75 kvp., with intensifying screens*

| TECHNIQUE | PAPER | FILM |
|---|---|---|
| *55 kvp.* | | |
| *Density* (under 12.7 mm. of aluminum) | 0.34 | 0.37 |
| *Contrast* (density change per mm. of aluminum) | 0.066 | 0.082 |
| *60 kvp.* | | |
| *Density* (under 12.7 mm. of aluminum) | 0.57 | 0.84 |
| *Contrast* (density change per mm. of aluminum) | 0.088 | 0.135 |
| *65 kvp.* | | |
| *Density* (under 12.7 mm. of aluminum) | 0.86 | 1.26 |
| *Contrast* (density change per mm. of aluminum) | 0.104 | 0.135 |
| *70 kvp.* | | |
| *Density* (under 12.7 mm. of aluminum) | 1.19 | 1.59 |
| *Contrast* (density change per mm. of aluminum) | 0.085 | 0.104 |
| *75 kvp.* | | |
| *Density* (under 12.7 mm. of aluminum) | 1.38 | 1.81 |
| *Contrast* (density change per mm. of aluminum) | 0.063 | 0.085 |

These data show that throughout the useful range the density and contrast obtained with film are greater than those obtained with paper for equal roentgenographic exposures. It would be necessary to decrease the X-ray tube voltage at least 10 kilovolts for paper in order to obtain equal contrast for paper and film. It would be necessary in addition to increase the milliampere-seconds for paper at least three times in order to get comparable densities for paper and film. Even with these drastic and impractical changes in technique the maximum observed density

on paper would not exceed 1.6, and the contrast for densities between 1.3 and 1.6 would be lower than those obtained with film. The sharpness obtained with paper would be less since it is necessary to increase the milliampere-seconds and therefore the focal spot size to obtain adequate contrast and density.

It may be concluded therefore that paper is technically inferior to film as a diagnostic material in chest roentgenography.

Portable apparatus requires the use of exposure times of 0.25 second to 1.0 second. This produces excessive unsharpness due to motion of the heart and the lungs. Many diagnosticians claim that this prevents accurate diagnosis. Others have stated that the parts of the lung in which the lesions of minimal tuberculosis are usually found move relatively little during exposure and that therefore the use of long exposure times for the production of roentgenograms in diagnostic surveys is not a serious disadvantage. This question is concerned with problems with which the diagnostician is most familiar and which therefore he alone can answer.

The fluoroscope produces images far lower in brightness than those obtained with either film or paper. Tests have been performed for the purpose of determining the brightness of the fluoroscopic image. A photoelectric cell was connected to an indicating meter. The deflection of this meter was found to be proportional to the light passing through the aperture in front of the cell. The diffuse light from a standard film illuminator through a film having a density of 1.7 produced a meter deflection of 6 mm. The photocell was held in front of a Patterson Type B fluoroscopic screen. With the X-ray tube operating at 85 kvp., 4 ma., and a focal spot-screen distance 30 inches, and *no object interposed between the tube and the screen,* no deflection of the meter connected to the photoelectric cell was observed. This negative result may be usefully interpreted as follows: it is quite certain that if the deflection had exceeded 0.2 mm. it would have been perceptible. Let it be assumed that it *was* actually 0.2 mm. Under these conditions it can be calculated that the brightness of the fluoroscopic screen with no interposed body between the tube and the screen was of the order of one-thirtieth of the brightness which is observed on the face of a film of density 1.7 placed before a film illuminator. Measurements with an ionization chamber show that the average intensity of the X-ray beam after passing through the chest of a normal adult is one-twentieth the intensity of the beam with no object interposed between the tube and the screen. If the

screen brightness is proportional to the intensity of the X-ray beam striking it, the average brightness of the screen during fluoroscopic examination of the chest is one-six-hundredth the brightness of the surface of a film of density 1.7 placed before a film illuminator. Data presented in the International Critical Tables show that the eye can perceive brightness differences of the order of 2.2 per cent for the film of density 1.7 held before the illuminator, while at the average level of brightness of the fluoroscopic screen the eye can see brightness differences only of the order of 30 per cent. Thus under a most conservative interpretation of the data the fluoroscopic image has contrasts greatly inferior to those obtained with film or with paper.

## SUMMARY

The material thus far presented leads to the following general conclusions:

1. It is necessary to use four-valve roentgenographic apparatus with suitable auxiliary materials including X-ray film to obtain roentgenograms of the chest of the highest quality known to-day. The cost of this equipment is approximately $3,500.00; it is bulky and therefore difficult to transport; it requires a supply transformer and line of high capacity for its operation.

2. Portable apparatus produces roentgenograms which are unsharp due to the motion of the parts within the chest during the long exposures which must be used with this type of equipment. It is easily transportable and does not require a large supply transformer or line. The cost is approximately $1,500.00.

3. The fluoroscope produces images greatly inferior in contrast and brightness to those observed in film or paper roentgenograms; it costs approximately $1,200.00; is easy to transport and to operate.

4. Roentgenograms on paper are technically inferior to those produced on film. If the contrast and average densities are equal the paper roentgenogram lacks sharpness because a large focal spot is required. The maximum density which can be produced on paper is limited to approximately 1.6 and the contrasts in the more dense parts of the roentgenogram area are much less than those obtained with film. Paper costs less than film.

## PROBLEMS WHICH REQUIRE SOLUTION

The choice of a diagnostic method at present depends chiefly upon factors which are not discussed in previous sections of this paper. The most important of these factors is a comprehensive analysis of the results of the work of experienced roentgenologists. The facts derived from such experience should determine the relative importance of the technical and economic factors from the diagnostic point of view. For example, granting that the contrast of the fluoroscopic image is inferior to that of the roentgenogram on paper or film, if this inferior contrast is sufficient for the diagnosis of minimal tuberculosis then the superiority of the film may be of no practical importance.

Questions have been sent to forty-five general roentgenologists, roentgenologists in tuberculosis sanatoria and health officers, asking their opinions concerning the various methods described in the first section of this paper. The results of the survey are given briefly below.

The questionnaire was prefaced by the following notes and instructions:

The use of roentgen methods for the diagnosis of tuberculosis and pneumonoconiosis continually increases. Owing to the intensive drive against tuberculosis it is becoming more and more common for agencies to examine school children throughout large areas in order to detect the presence of tuberculosis at an early stage. New compensation laws have led to the use of roentgen apparatus for the examination of industrial workers to detect the presence of tuberculosis or pneumonoconiosis. These mass surveys bring forth a number of problems in which scientific and economic questions are interdependent. This situation should be kept in mind in answering the following questions.

Please indicate in the attached table your choice of methods for the purposes presented in the table. Under Questions 1, 2, 3 and 5 indicate the relative merits of the various procedures by marking your first choice 1, your second choice 2, et cetera. Questions 4 and 6 may be answered by recording the estimate under each procedure. If, after you have answered the questions in the table, you wish to discuss any pertinent points please use the space below.

The questionnaire itself is in tabular form. The following methods were listed:

(*1*) Stereoscopic p.-a. roentgenograms of the chest on film made with accepted modern technique

(*2*) Single p.-a. roentgenograms of the chest on film made with accepted modern technique
(*3*) Single p.-a. roentgenograms of the chest on film made with long exposure, low current technique
(*4*) Single p.-a. roentgenograms of the chest on paper using modern technique
(*5*) Fluoroscopic examination of the chest using modern screens

The roentgenologists were asked to choose the relative value of each of these methods for each of the following objectives:

(*1*) Order of diagnostic merit regardless of cost (early tuberculosis)
(*2*) Order of diagnostic merit regardless of cost (early pneumonoconiosis)
(*3*) Order of choice for county or state survey of school children with due regard to cost (tuberculosis)
(*4*) Probable number of cases missed out of 1000 diagnoses made under survey considered in Question 3 (tuberculosis)
(*5*) Order of choice for survey of industrial workers with due regard to cost (pneumonoconiosis)
(*6*) Probable number of cases missed out of 1000 diagnoses made under survey considered in Question 5 (pneumonoconiosis)

It is not the purpose of this paper to present in detail the answers to this questionnaire. The following facts, however, are important to the present discussion and should be noted carefully. Thirty-three roentgenologists who answered desired stereoscopic roentgenograms of the chest made according to modern techniques for the diagnosis of either tuberculosis or pneumonoconiosis if cost were not considered. Four of the thirty-three specified further that they did not believe this to be sufficient. They would like, in addition, to make a fluoroscopic examination and lateral or oblique roentgenograms in order to guarantee as well as possible a correct diagnosis. This result might of course have been expected since practically all roentgenologists recognize the value of technically adequate stereoscopic roentgenograms if they can be made.

For surveys of large numbers of school children or industrial employees opinions differ greatly. For tuberculosis surveys the following summary is adequate for the present purpose. The methods given first or second choice by any roentgenologist were separated from the remaining answers. If a method is chosen first it is given a score of 2. If a method is chosen as second best it is given a score of 1. The results of this tabulation for tuberculosis surveys among school children are as follows:

*Surveys of school children for the diagnosis of tuberculosis*

| DIAGNOSTIC METHOD | TOTAL SCORE BY 33 ROENTGENOLOGISTS (FIRST CHOICE, SCORE 2; SECOND CHOICE, SCORE 1) |
|---|---|
| Stereoscopic p.-a. roentgenograms of the chest on film made with accepted modern technique | 10 |
| Single p.-a. roentgenograms of the chest on film made with accepted modern technique | 40 |
| Single p.-a. roentgenograms of the chest on film made with long exposure, low current technique | 14 |
| Single p.-a. roentgenograms of the chest on paper using modern technique | 19 |
| Fluoroscopic examination of the chest using modern screens | 10 |

In the case of surveys of industrial workers for the detection of pneumonoconiosis the scores obtained in a similar manner are as follows:

*Surveys of industrial workers for the diagnosis of pneumonoconiosis*

| DIAGNOSTIC METHOD | TOTAL SCORE BY 33 ROENTGENOLOGISTS (FIRST CHOICE, SCORE 2; SECOND CHOICE, SCORE 1) |
|---|---|
| Stereoscopic p.-a. roentgenograms of the chest on film made with accepted modern technique | 21 |
| Single p.-a. roentgenograms of the chest on film made with accepted modern technique | 40 |
| Single p.-a. roentgenograms of the chest on film made with long exposure, low current technique | 10 |
| Single p.-a. roentgenograms of the chest on paper using modern technique | 9 |
| Fluoroscopic examination of the chest using modern screens | 6 |

Most of the surveys of school children now being conducted are made either with portable apparatus or with roentgenographic paper. This would seem to be at variance with the opinions of the roentgenologists who answered this questionnaire. It should be noted also that these roentgenologists believe that it is much more important to obtain accurate high quality films for the diagnosis of pneumonoconiosis than it is for the detection of tuberculosis among school children. The fact that long exposure times (portable apparatus) are so often used for chest roentgenographic surveys is particularly pertinent when it is noted that, in this questionnaire, out of a total score for tuberculosis surveys of 93 only 14 points are scored for portable apparatus, while for surveys for pneumonoconiosis the proportion is similarly low.

Some of the roentgenologists who answered these questionnaires wrote

notes on some aspects not included in the questions. There were comments from about one-fourth of the total which show that these men believe that the ability of the interpreter is one of the most important factors in a diagnostic survey. It is this fact which makes the entire problem so difficult to solve from a practical point of view. Perhaps it is worth while to consider methods for testing the ability of the diagnostician engaged in survey work, and perhaps this work should precede any discussion of the relative merits of the several methods.

There have been several carefully controlled scientific tests of the adequacy of roentgenographic paper and of the fluoroscope for the diagnosis of tuberculosis and pneumonoconiosis. These tests have been described in several papers published in medical journals. In general these papers show an objective approach to the problem at hand. The conclusions are carefully stated in terms which cannot be misinterpreted by an intelligent reader. It is from work of this type that standards for diagnostic surveys must be constructed. Those who have made these carefully controlled tests are now in a position to judge accurately the relative merits of the methods under consideration. It may be supposed, however, that roentgenologists with less experience are less able to use these methods and that therefore their results may be less accurate.

There are two questions concerning apparatus which is now used extensively for chest roentgenographic surveys which require further consideration: (*1*) Is roentgenographic paper used for many surveys because it is technically adequate, or because the methods developed for its use are fast and inexpensive? (*2*) Would the production of improved portable roentgenographic apparatus extend the usefulness of the diagnostic method?

Roentgenographic paper, cut to 14 inch by 17 inch sheets and mounted in cassettes for exposure, is used relatively little. The greatest number of chest roentgenograms on paper are made with the special apparatus developed by the Powers X-ray Products, Inc. A roll of paper is loaded in a light tight container so arranged that 14 inch by 17 inch areas may be successively brought into contact with an intensifying screen in back of the panel before which the patient stands. After the roll is exposed it is processed automatically in a machine designed for this purpose. After drying it is once more rolled and placed in a special viewing device where each roentgenogram may be examined by the diagnostician. This method is convenient, time-saving and economical. In addition, the storage of the rolls of paper requires less space than the storage of

an equivalent number of single 14 inch by 17 inch films in envelopes. If the paper is adequate from the diagnostic point of view this general method satisfies all important requirements. On the other hand, if the paper is not adequate it would be logical to consider using roll film with the special apparatus devised by the Powers X-ray Products, Inc. It would then be possible to combine (*1*) the technically superior qualities of roentgenograms on film, and (*2*) the time-saving and economical methods now used for producing roentgenograms on paper in rolls.

Portable apparatus at the present time lacks accurate means for timing the roentgen exposure, precise control of X-ray tube current and suitable means for varying in small steps the X-ray tube voltage. Perhaps before condemning the portable apparatus it would be worth while to construct an improved portable equipment which would possess the factors which are at present missing. The Moore School X-ray Laboratory has prepared specifications for such portable equipment. This apparatus would permit the variation of X-ray tube voltage at will in steps of one kilovolt. The X-ray tube current would be constant regardless of changes in line voltage. Exposure times of the order of 0.25 second could be used. The apparatus could be packed into the back of a sedan by one person and could be set up and operated without difficulty by one person. If it is deemed advisable to develop this apparatus for use it can be done.

## CONCLUSIONS

The authors believe that conditions have arisen which require the formulation of definite criteria for the choice of diagnostic X-ray methods for surveys. They believe that such criteria may be formulated by a Committee of the American Sanatorium Association in collaboration with representatives from the American Roentgen Ray Society and the Radiological Society of North America. A list of the relative merits of the various methods for diagnosing tuberculosis might be prepared. This would serve chiefly as a guide for health agencies and others who are interested in making mass surveys in order to detect cases which should be treated and to investigate contacts which may have caused these cases. The formulation of criteria of this nature depends in part upon technical factors, and these are presented briefly in this paper. It depends in much larger part upon questions which must be answered by diagnosticians. Perhaps through careful collaboration a group of roentgenologists might answer such questions in a clear concise manner

useful to those who are planning chest roentgenographic surveys. Some of these questions are listed below.

(*1*) Is it better to survey a large number of possible cases by means of a low-cost method, or to survey a smaller number by means of a high-quality method which costs more? Or, is it better to combine two methods?
(*2*) Under what conditions, if any, should the fluoroscope be used as a method of diagnosis?
(*3*) Under what conditions, if any, should paper be used as the roentgenographic material?
(*4*) Are stereoscopic pairs or oblique views necessary in preliminary surveys?
(*5*) Is there need for the development of portable apparatus which would produce comparable roentgenograms with an exposure time of 0.25 second?
(*6*) Is there a place for companies like the Powers X-ray Products, Inc. and Precision Radiographs, Inc., who make roentgenograms in large numbers to be interpreted by the roentgenologist who employs these firms, to make the films? Under what conditions should one of these services be used instead of purchasing new equipment?
(*7*) Is there a method whereby the diagnostician who plans to interpret the results of a survey might be examined to determine whether he is competent to do this work?
(*8*) Is there need for the development of a fast roentgenographic method employing roll film?

## REFERENCES

(1) Wilsey, R. B.: The physical fundamentals of chest roentgenography, Amer. Jour. Roent. & Rad. Ther., 1933, *30*, 2, 3 & 4.
(2) Weyl, C., Warren, S. R., Jr., and O'Neill, D. B.: The choice of certain technical factors for chest roentgenography, Ibid., 1936, *35*, 534.
(3) McPhedran, F. M., Weyl, C., and Warren, S. R., Jr.: Practical applications of contemporary research on X-ray apparatus and technique for the chest, Amer. Rev. Tuberc., 1937, *35*, 208.

# AUXILIARY TECHNIQUES IN CHEST ROENTGENOGRAPHY[1]

CLARENCE J. ZINTHEO, JR.

Roentgenography of the chest, not unlike that of other parts of the body, is an art and a science. By science of chest roentgenography is meant the study of such things as exposure factors, selection of focal spots, use of the high-speed Potter-Bucky diaphragm, standardization of dark-room technique, selection of intensifying screens and other technical phases dealing with the production of the roentgenogram. By the art of roentgenography, on the other hand, is meant the management of the patient in different ways to reveal information of the greatest use to the diagnostician. This part ordinarily is considered rather simple and yet a compilation of the variations mentioned in a rather limited file of literature shows it to be much more extensive than at first thought. Knowledge of the various procedures and their special uses should be of value to the phthisiologist and aid his requests to the X-ray department for assistance.

## THE STANDARD POSITION

A standard position for chest roentgenography has been widely accepted and leaves but a few minor details for discussion. The patient stands or sits upright, facing the plate with the chin elevated over the top edge of the cassette or the approximate ledge of the cassette holder and rotates the scapulae as far as possible out of the lung fields. Where the cassette holder permits, this may be best accomplished by wrapping the arms of the patient around the cassette in front of him, thus not only pulling the scapulae outward but also increasing the stability of the patient in his position. Where conditions do not permit this, the hands are usually placed on the hips and the elbows rotated forward. When the hands are spread open on the hips with the thumbs forward and the fingers backward the clavicles are lifted slightly over the projection in other positions and so tend to obscure partially the projection of the apices, for which reason this placing may be less desirable. A

[1] From the Firland Sanatorium, Richmond Highlands, Washington.

posture with the fingers well forward and thumbs back, or with the back of the wrist against the hips, is usually better. Between the latter two positions there is little to choose. That with the back of the wrist against the hips tends to throw the elbows forward, and so remove the scapulae from the fields more naturally, but unless the waist is deep there may be a tendency to slip off. With the fingers to the front and thumb back, the position is well settled if the technician is attentive to instructing that the fingers reach well forward, and careful that the shoulders are relaxed and dropped, for otherwise the patient may have a tendency to hunch them high and so raise the clavicle over the apices.

In roentgenography for tuberculosis it is usually better to centre the tube to the 7th to 9th dorsal vertebrae, for in this direction the apex is more clearly projected above the clavicles. Where interest is focused on the bases of the lung and the apices are of secondary importance, centering on the third dorsal vertebra will better reveal a portion of the anterior costophrenic sulcus.

If it is desired to study the posterior costophrenic sulcus in the standing position, a projection from anterior to posterior is used and the ray centred toward the suprasternal notch, but in this direction the advantage of ray divergence in displacing the scapular shadows out of the pulmonic field is lost and it is seldom possible to eliminate some overlapping. This is one reason for the adoption of the dorsoventral as the standard projection.

A focal film distance of five to seven feet is customarily employed for the standard position. Meyer (31) makes use of the principles of ray divergence and advocates closer distances to aid in the localization of pathological conditions by taking two films, an anteroposterior and a posteroanterior, on each patient at a three foot distance. When the principles of divergence are well understood and the difference in geometric unsharpness of those portions of the lung nearest to the film as compared to the shadows of those more distant is considered, this method of study has its advantages. Meyer demonstrates its value in defining an encapsulated effusion on one of his cases as being situated at the parietal pleura rather than being a concealed interlobar effusion.

The best transillumination of the lung is obtained when the exposure is made at inspiration and consequently this phase has been adopted as the standard. A few experiments on transillumination conducted at this laboratory indicate that there is little difference between the density of the upper lung fields whether the exposure is made during moderate

inspiration or the chest be forced to its maximum expansion, but that there is considerable difference in the density of the lower lung fields between the two conditions. It is suggested, then, that where the interest is directed to tuberculous infiltrations, considering the possible danger of rupturing newly formed fibrosis by forced inspiration, the patient be merely instructed to inhale and hold his breath rather than to stress deepest inspiration.

### STANDARD POSITION IN EXPIRATION

A roentgenogram made in expiration is sometimes quite useful to demonstrate the presence of a small pneumothorax which would escape detection when exposure is made at the height of inspiration. In the paper by Greenberg (20) calling attention to this procedure, the illustrations show its value beautifully. He attributes the superiority of the expiratory film to the fact that the volume of the pneumothorax remains practically constant during respiration while the area of the pleural sac is altered. The change in the surface area incident to respiration produces changes in the distribution of the pneumothorax with the layer of air about the lung becoming thinner on inspiration and thicker on expiration; where sometimes the shadow cast by a thin layer of air on inspiration may be obscured by the shadow of the lateral chest-wall, the thicker layer of air on expiration is easily seen. Because the mass of lung structure is projected over a smaller surface area at expiration than at inspiration, thus increasing the density which must be penetrated, and perhaps because of other influences, it is necessary to give a slightly greater exposure to the expiratory than to the inspiratory roentgenogram in order to maintain equal film densities. The increase usually needed is from 2 to 5 KV.

In the study of mediastinal shift in pneumothorax, Matson (29) advises the use of films in expiration.

The expiratory roentgenogram, when compared with an exposure made during inspiration, may be used, according to Dehn (10), to detect the presence of pleural adhesions. He states that in the presence of adhesions the intrapulmonary shadows move during expiration in the same directions as that taken by the ribs, whereas without adhesions the movement is in a direction opposite to that taken by the ribs.

The appearance of the vascular system varies with the degree of inspiration, and to prevent a faulty interpretation the diagnostician must have some idea of the respiratory level at which the exposure was

made. A simple way for determining the degree of inspiration at which a chest film was exposed has been worked out and described by Allen, Waltz and Hanner (1). The method consists of measuring the distance from the sternal end of the clavicle to the midpoint of the dome of the diaphragm and comparing this with the lateral chest width at the diaphragmatic level. When the clavicular-diaphragmatic distance equals two-thirds to three-fourths of the width of the chest the plate represents approximately complete inspiration, and when it is only half the width of the chest, complete expiration.

Fray (16) calls attention to the fact that at maximum expiration the lower lungs are so deflated that the diaphragmatic shadows are nearly obscured in normal cases, but with emphysema it is a common finding that they remain brilliantly outlined due to the increase of residual air.

### DOUBLE EXPOSURE ON ONE FILM, ONE IN EXPIRATION AND ONE IN INSPIRATION

To record the respiratory excursion of the diaphragm, Thomas (40) suggested that two exposures be made on the same film at each of the positions of maximum excursion. The technique for each exposure in this procedure is reduced in order to maintain the total density of the film within reasonable limits; a very light exposure is given at maximum inspiration, but with the diaphragm elevated during expiration its shadow protects that previously made and so greater intensity may be used on the second exposure made at forced expiration. Fray (17) modifies the method by using a brass filter to cover the lower half of the chest during the inspiratory exposure. Thomas reports that the technique has been very satisfactory in checking the movements of the diaphragm in postoperative conditions where the diaphragm has moved physiologically, but also suggests (41) that instances may arise where the diaphragmatic movement is slight, if any, or may be paradoxical. Under such conditions only one diaphragmatic outline is seen on the film and the observer may be at loss to know whether there has been an error in technique or whether some abnormal conditions are actually present. To obviate such confusion he designed a shutter grid consisting of strips of sheet lead, one-sixth of an inch in width, spaced one-sixth of an inch apart upon a sheet of aluminum and sloping at 45° toward the midline. This is mounted in a housing to be placed between the patient and the film, with appropriate stops to permit shifting of the shutter such an amount that in one position the shadow of the lead strips

will be superimposed upon a previous exposure through the window spacings. The device is placed between the patient and the film and exposure made at full inspiration. The grid handle is then drawn out to the appropriate stop and a second exposure is made at full expiration. The conglomerate mixture of densities which appear upon the developed film may be resolved by connecting positions of the diaphragm on alternating bands with a skin pencil.

The pulmonic areas measured by a planimeter on the film obtained by exposures at two respiratory limits is used by Fray (17) in predicting the various levels of pulmonary ventilation which would be normal for the individual. Results so obtained compared with the values observed from spirometric measurements give data on the degree of respiratory impairment which may be of considerable use in tuberculosis, especially when surgical procedures are contemplated.

The X-ray estimate of functional disability by measuring the areas at maximum inspiration and maximum expiration is also useful as an aid in the differential diagnosis of pneumonoconiosis.

### STANDARD POSITION BUT DENSE EXPOSURE

In bronchography the difference in absorption between bronchi filled with radiopaque fluid and the adjacent structures is sufficiently high that a greatly increased exposure may be used to advantage because it not only gives better contrast, but it is also necessary to prevent a possible loss of fine detail due to underexposure, or of shadows behind the diaphragm. An increase of three to four times over normal may well be used which may be most conveniently realized through doubling the time and adding 10 KV. Because on a bronchogram in the standing position attention is directed to the lower lung field, the tube should usually be centred high, say to the third dorsal vertebra. Parenchymatous infiltrations are usually not of major interest during such a study and so the consequent burning out of the pulmonary structure is not objectionable.

Some cases of tuberculosis show local areas of dense pathological conditions which are not sufficiently penetrated by the normal exposure to reveal possible hidden cavities. On these a roentgenogram made with from 10 to 20 KV increase over the normal may reveal conditions which would otherwise go unnoticed. Ordinarily an 8-inch to 10-inch film to cover just the region of interest will be sufficient for the purpose and

save the expense of a larger size, the major portion of which would be wasted. Jones (24) has called attention to the need of this procedure in discovering fenestration or defects of ribs which may simulate pulmonary cavities when the abnormality overlies a pulmonary lesion.

### DISSIMILAR EXPOSURE OF EACH HEMITHORAX

The phthisiologist frequently meets conditions where the radiopacity of one hemithorax is different from that of the other. Thoracoplasties, large pleural effusions, massive atelectasis and similar conditions may require a large increase in a radiographic exposure to reveal underlying conditions. Frequently a better visualization of the lung structure may be obtained through a thickened pleura or dense lesions by a small increase in exposure over the normal. To obtain radiation quality correct for each hemithorax, two films may be made using the correct conditions for each side, but because half of each film is wasted and because it is somewhat of a nuisance to have the extra film, numerous attempts have been made to permit taking the roentgenogram in such a way that proper penetration to each side is secured on one film. Determann (11) Allison (2) and Wiese (45) suggest the use of metallic filters over the normal hemithorax to reduce the overexposure from an increased penetration used on the dense side. Gershon-Cohen (19) and Fuchs (18) have employed a plastic filter for this purpose mounted at the X-ray tube stand in such a way that it will reduce the radiation to half of the film. These measures suffer from two handicaps. Although the radiation to the normal hemithorax may be reduced in quantity to give the proper photographic density by filtering a high output of a harder quality, this gives films which are distinctly inferior from the standpoint of contrast. Also there is an appreciable degree of inflexibility to the method because the exposure increase must be balanced to the thickness of the filter used, and so it is necessary to employ only a prescribed increase or to maintain a considerable assortment of filter thicknesses.

The method suggested by Sampson (34) consists of covering half the cassette with sheet lead while exposing the normal side and then placing the film in a Bucky with the other half covered and exposing the dense side to an increased Bucky technique. This obviates not only the above difficulty but takes advantage of the better results which may be obtained through dense structures when employing the Bucky to reduce the increased scattering. The appearance of films so obtained may be distracting to some due to the unequal sizes of the hemithoraces caused

by the unequal enlargement at different focal-film distances. Also the necessity of repositioning patient and X-ray tube for the two exposures on one film may be objectionable in a busy laboratory because it is time consuming.

Perhaps the simplest and most flexible method of accomplishing dissimilar exposures of each hemithorax consists of a small shutter operating in one of the filter slots of the tube stand in conjunction with a rectangular diaphragm which projects a cone of rays only slightly larger than the X-ray film (48). This shutter is so arranged that it will alternately cut off the rays from first one and then the other half of the film. By its use complete flexibility of exposure conditions is possible, varying from an increase of only 2 to 4 KV for a slightly thickened pleura to any desired heavy penetration on patients having one dense side. When this shutter is controlled by a string from the control room it is frequently possible to make the exposure of one side, shift the controls and the shutter and expose the other side in a period of less than 5 seconds while the patient holds one breath. When more time is needed there is no objection to allowing the patient to breathe between exposures so long as he does not change his position. Once it is prepared, this accessory is suitable for all cases where dissimilar exposures of each hemithorax is desired.

## STEREOSCOPIC EXPOSURES

Stereoscopy has been extensively studied and a number of papers dealing with the conditions of making and viewing the exposures have appeared in the periodicals. It is not the purpose of this paper to introduce a discussion of the relative merits of flat films *versus* a stereoscopic pair in the diagnosis of tuberculosis; Sante (35) Wessler and Jaches (44) and Exner and Rigler (13) have voiced opinions upon this subject. Aside from its value in the interpretation of lesions, stereoscopy is useful to the phthisiologist in localizing the depth of cavities or other intrathoracic structures as a guide to surgical interference. A method whereby the actual depth of the cavity beneath the anterior and posterior ribs may be derived has been outlined by Johnson (23); it is a little too detailed for presentation here, but those who are interested may refer to the original paper. Precautions to be observed in preventing faulty interpretation have been investigated and discussed by Sweany, Kegerreis and Cook (39) by Wilsey (46) and by Ferguson (14).

### STANDARD OBLIQUE POSITION

Four oblique positions are standard for the demonstration of conditions which may not be clearly defined in the usual view. In each one the relationship of tube and film remains the same with the central ray normal to the plane of the film and the patient is rotated, usually 45°, to the right or left from an anteroposterior or a posteroanterior position (36). Oblique views are best made with attention directed only to the hemithorax nearest the film, because of the increased unsharpness and the distortion of the shadows of the other side. The plate divider can be used for making both an anterior and a posterior oblique exposure along side each other on a single film, which facilitates the study of the results and saves an extra film.

In positioning for the anterior oblique position the hand of the side next to the film is placed on the hip and the shoulder is drawn back so that, with the body at an angle of 45° to the film, the anterior axillary portion of the hemithorax is against the plate. For the posterior oblique position the back of the wrist is on the hip to throw the shoulder forward, and the patient faces in the direction of the X-ray tube, with the body at an angle of 45° to the film and with the posterior axillary line against the cassette. Where two oblique views of one hemithorax are taken with the use of the plate divider, the arm on the side away from the film may be relaxed by the side, but if it is desired to show both sides of the chest, the distal arm should be held over the head to grasp the opposite ear or a part of the cassette holder.

To serve as a guide in the accurate placement of oblique views small triangles may be cut from heavy cardboard; with the base against the cassette the hypotenuse across the patients chest or back will define the position fairly accurately. If considerable work of this nature be done it may be more convenient to use the frame described by Banyai (4) which attached to the cassette holder guides the patient to the correct position.

One of the most frequent needs for the oblique positions is to determine pneumothoraces partially or wholly limited to the anterior or posterior aspect, and especially to study adhesions. As a preliminary for intrapleural pneumolysis both an anterior and a posterior oblique roentgenogram of the affected side are necessary and should be routine procedures in order to reveal adhesions which cannot be seen in the posteroanterior position, and to show the true condition of an adhesion visible in the posteroanterior but which runs obliquely. Ellison (12) and Haight and

Pierce (21) call attention to this use of the oblique view, the degree of rotation for which should be determined in the fluroscope. They suggest that advantage be taken of the stretching of adhesions to their full length during expiration by making the exposure during maximum expiration, a procedure which will necessitate an increase of 2 to 4 KV over what would be given during inspiration.

In the preliminary study of adhesions before pneumonolysis it is advantageous to make exposures in a number of slightly different oblique positions. At this institution, rotations of 15°, 30° and 45° are ordinarily used, the angles being controlled by the cardboard triangles mentioned. Stereoscopic films of the oblique position are also advocated and these, as well as flat plates, can be obtained with the divider at a saving of films by making the two exposures of one view with one half the film area covered, shifting the divider and resetting the cassette changer and then exposing the other position on the other half of the film. The oblique positions are also needed for the study of mediastinal hernia in pneumothorax; for this purpose it is necessary to expose the entire chest onto a single film.

Pancoast and Pendergrass (33) state that the oblique view displaces the shadows of pectoral muscles, brings out the peaking of the domes of the diaphragm, and demonstrates slight thickening of the pleura which may be overlooked in the ordinary roentgenograms. This is particularly true in cases of asbestosis where thickened pleura largely accounts for the symptoms which are out of proportion to the parenchymatous changes.

Fray (16) uses the ratio of the transverse diameter of the chest in the posteroanterior to the left anterior oblique positions as an aid in the diagnosis of emphysematous deformity of the cage, which, at times, is a useful confirmatory sign.

Sometimes the oblique positions are valuable in the differential diagnosis of encapsulated pleural and interlobar effusions, especially if the most revealing angle is first determined fluoroscopically. At the same time it may be found that greater information is obtained by centering the tube higher or lower than normal.

### ANDRUS TECHNIQUE

The Andrus technique (3) is an oblique exposure in which the plane of the film remains in contact with the anterior or posterior chest-wall, while either the tube is moved laterally a certain distance to give a

known angle of projection, or the patient and plate are both rotated from the perpendicular to the central ray. The advantage of the Andrus technique lies in the ease of obtaining a high degree of precision for positioning to any desired angle of rotation. Accuracy of rotation allows the exposure to be made at the correct angle to disclose the fullest amount of otherwise hidden pulmonic fields near the margin anterior to the mediastinum and in the paravertebral fossae.

Differences in shadow projection determine to a large extent whether the oblique exposure should be made with the standard method or by the Andrus technique. With the film remaining perpendicular to the central ray and the patient rotated, except for the slight enlargement of shadows caused by ray divergence, magnified distortion cannot be obtained and pneumothorax adhesions, for example, are not seen longer than they really are, although in all but one critical position they will be foreshortened, whereas with the Andrus technique adhesions can be either foreshortened or magnified, depending upon the geometrical arrangements, an effect which may sometimes be undesirable and sometimes advantageous. On the other hand, when the film remains parallel to the frontal plane of the patient's body, the structures which are parallel to this same plane are projected in nearly their normal relationships; with the Andrus technique the trachea and the main bronchi are seen in nearly true posteroanterior projection, but without the shadows of spine and sternum superimposed to confuse the picture. Because this projection gives such a beautiful picture of the tracheal bifurcation instead of the overlapping of bronchi obtained with the standard oblique views, it is much preferred for the study of tracheal and bronchial stenosis, of peritracheal and peribronchial adenopathy, especially after calcification has started, of the carina and of the angular relationships between the trachea and the main bronchi.

### LATERAL VIEW

The shadows of the mediastinal structures and of the lung most distant from the film, superimposed upon that of the lung next to the film, when exposed in the lateral view so confuse and obliterate the markings that a study of fine detail in this position is usually of little value, but where gross changes are to be studied this view is so useful that it should be frequently employed.

In exposing the lateral view the patient is usually instructed to cross his forearms so that each hand grasps the opposite elbow and then to

raise them so that they lie across the top of his head. He is then placed in the true lateral position with the body centred to the film and is told to straighten his body so that the spine is in as nearly normal contour as possible. The affected side rests against the film to aid in support and, when available, a compression band may be drawn across the chest to stabilize an unsteady posture. Where much lateral roentgenography is done it might be better to fasten a short bar rigidly, protruding outward from the cassette holder sufficiently high above the patient's head that the patient must stretch his arms upward to reach it. When firmly grasped with both hands this should aid in holding the patient steady and permit a more comfortable posture and a complete removal of the arm and shoulder shadows from the lung field. It is usually stated that an increase of four times over the standard posteroanterior exposure is required for laterals, but this may vary somewhat with the character of the normal; if low voltage is used an increase of at least 10 KV may be needed for the lateral in addition to a three- or four-fold increase of time.

It should be noted that when the body is in true lateral position and centred to the plate so that the central ray passes through midway between the anterior and posterior surfaces, the projection of the posterior ribs on the side most distant from the film will not superimpose the shadows of those nearer to the film, but will usually be about 2 to 3 cm. farther out.

Usually cavities in nearly all parts of the lung, except in the very apex, may be demonstrated in the lateral view and so defined as to their depth in the chest, which information is of decided value to the thoracic surgeon preceding operative measures. The lateral view is also extensively used to localize gross lesions in a lobe or to differentiate between dense lobar and interlobar shadows. This purpose is well illustrated by Levitin and Brunn (27) by Warfield (42) by Hampton and King (22) and by Stivelman (38). In the study of interlobar effusions it may be best to examine the patient with the fluoroscope first to determine at what height the X-ray tube will best project the shadows. The lateral position is also useful for revealing enlargement of the lymph nodes in front of and below the bifurcation of the trachea and to demonstrate atelectasis of the lower lobe. It is necessary for a complete study of the diaphragm, especially for the visualization of small pleural effusions and adhesions. Empyema pockets injected with lipiodol should be studied in the lateral as well as in other positions. A lateral exposure in addition to others is usually considered essential for a complete bronchographic study.

### FLEISCHNER POSITION

In the lateral exposure an interlobar effusion of considerable quantity can be recognized as an oblong or ovoid shadow running obliquely downward and outward from the lung root, seen through the cardiac density. But if the effusion is small, or if there are considerable lesions overshadowing the region, it will not be visualized. A valuable method of projecting a shadow of interlobar effusions with the rays tangential to the plane of the septum, but without obfuscating the shadows of the heart or lesions in the contralateral lung, has been described by Waters (43) who ascribes its origin to Fleischner. In this position the patient stands away from the film, which is held vertical and perpendicular to the central ray, and faces the tube and then bends backwards in an extreme lordosis until the back of the neck rests on the upper edge of the cassette and the body slopes forward at an angle of about 45°. An exposure of from two to three times the normal is then made.

Although the angle of the plane of the interlobar septa with the body axis is not constant in all people, a slope of 45° will usually be satisfactory for the purpose; a small triangle of cardboard fitted with one edge against the cassette and the hypotenuse against the patient's back will aid in obtaining the correct slope. If the volume of work justifies, a sloping frame, such as is illustrated in Waters' paper, against which the patient reclines, may be hung on the cassette holder. Where more precise angulation is desired a preliminary study with the fluoroscope is indicated.

In the standard position an interlobar effusion will cast a shadow of apparent consolidation with the hazy edges fading out into the surrounding tissue, but in the Fleischner position it will appear as a triangular density with the base toward the hilum and apex in the midlung field, the edges of which are sharply defined.

This technique has also been described by Miller (32) who calls it the McNeil position.

### BAUM'S APICAL TECHNIQUE

The phthisiologist not rarely sees a routine film which suggests the possibility of infiltration or even small excavation obscured by the superimposed shadows of the clavicle and ribs. An exposure made in such cases with the Baum technique (5) will definitely rule out or demonstrate the presence of a condition which is otherwise uncertain. The apical position is only occasionally called for, but on those cases in which it is

indicated the information obtained is of considerable value. The first apical film that reveals a much more extensive involvement beneath the shadow of the clavicle than that suspected from the normal exposure may be quite startling. Baum also feels that the position is routinely indicated in the study preceding intrapleural pneumonolysis.

To make the exposure, the patient sits on the table resting his back against a wooden "pillow" sloped at a 50° angle, holding by the weight of his body a medium sized film crossways and high up beneath the back. The central ray is then directed at an angle of 10° from the vertical toward the suprasternal notch. The exposure made with this posture throws the shadows of the clavicle entirely above the lung fields and tends to concentrate markings in the lung by foreshortening them, thus not only revealing but accentuating faint shadows which otherwise might be obscured.

### THE PATIENT RECUMBENT

Cases are met in which it is necessary to make the exposure in the supine position because the patient is too ill to sit up or because of recent haemoptysis. The differences in the normal lung markings with the patient recumbent as compared with the patient standing make it necessary to be cautious in the interpretation of the finer shadows on films of recumbent patients, but gross morbid changes, such as a pneumonic reaction, an atelectasis and the shadows which sometimes indicate from which side a haemorrhage comes, will often be of sufficient value to justify the comparatively slight disturbance of the patient necessary to make such exposures. With the lessened ventilation in recumbent posture a slight increase in exposure technique of the order of 2 to 4 KV or a small change in time is usually needed.

The value of this position in shifting an unusual pleural effusion, simulating the diaphragm, so as to reveal the normal diaphragmatic contour is demonstrated by Yater and Rodis (47). When women with heavy breasts lie on their backs the mass of tissue flattens out over the chest and toward the side so that plates taken in supine posture will often reveal light infiltrations in the basal part of the lungs which might be obscured by the increased exposure necessary to penetrate that region when the patient is standing.

Bronchographic study of the middle and upper lung regions are satisfactorily made with the patient supine. If the oil be injected with the patient recumbent and slightly rolled to the affected side a film may be

placed on the table onto which he may roll over with very little disturbance for the exposure.

Korol (25) uses the prone position with tubes centred over the last rib to visualize the lower lung line as an aid in the study of emphysema with or without contralateral atelectasis or fibrosis.

### LATERAL DECUBITUS

With the patient radiographed while reclining in lateral decubitus, advantage is taken of the force of gravity to shift fluid or sometimes the heart to a different position than that occupied while the patient is standing, and thus revealing shadows that are otherwise obscured. When the exposure is made with the afflicted side down small pleural effusions which otherwise would be hidden by the diaphragm come into view, and it is sometimes found, as demonstrated by Brown (9), that such effusions are actually considerably larger than appeared. Bowen (8) and Korol and Scott (26) also advocate this method for studying pleural effusions. To make the exposure, the patient lies on his side in true lateral decubitus having either pillows, or better, the platform devised by Brown, to raise his body off the table and leave space for the shoulder. It is important that the cassette be low enough to include all of the lung field on the film and not to cut off the margin to which interest is directed. Brown's platform automatically takes care of this, but where this is not available it sometimes helps to place the patient up to the outer edge of the table so that the cassette may be held low; he may be supported by an attendant. His arms are wrapped around the cassette and the central ray directed toward the upper dorsal vertebra. In this position the recumbent lung is relatively small and airless while the upper is emphysematous so that the densities of the two hemithoraces on the roentgenogram are not equal: where attention is directed to the upper lung a decrease of 2 to 4 KV from the standard technique should be made in the exposure, while if the lower is under consideration, an increase of 4 to 6 KV should be given.

When the affected side is up the heart and mediastinum tend to shift away from the involved side, thus revealing areas which might have been obscured, while if fluid is present it shifts away from the lateral margin of the chest to permit study of this region and the outer part of the diaphragm. In hydropneumothorax this procedure may sometimes demonstrate only partial collapse of the lower lung which, when covered by fluid in the standing position, might have been assumed to be completely compressed.

The relatively emphysematous condition of the upper lung in lateral recumbency gives, according to Korol (26), a clear outline of cavities, small pneumothoraces and tumors, while re-aeration of localized atelectatic areas accompanying pathological foci better reveals the underlying lesions.

The lateral decubitus position is used, with slight modification, for bronchography of the upper lobe of the dependent lung by the transnasal method of Forestier and Leroux (15), the roentgenogram being exposed immediately after the injection is completed without disturbing the patient.

Examination of patients with selective pneumothorax in this position, with the affected side up, have revealed such significant changes to Blady and Cohen (7), that they believe that the "present day concepts of so-called selective pneumothorax must be modified." But even more important, the administration of pneumothorax treatment under fluoroscopic guidance in lateral decubitus has proved of inestimable value in difficult cases and permitted continuation of treatment which otherwise would have been discontinued.

Matson (30) studies oil injections to stiffen a labile mediastinum in pneumothorax with herniated lung, by exposing in the lateral decubitus with the pneumothorax side up.

### MISCELLANEOUS SPECIAL METHODS

In some disease processes of the lung the position of the diaphragm may be obscured or uncertain unless special methods are employed. For instance, patients have been met with in whom the success of phrenic surgery on the left side could not be proved due to dense shadows in the lower part of the chest, but repeated operation was avoided by giving Seidlitz powders. The gas liberated in the stomach outlined the lower surface of the diaphragm and permitted the necessary tests and observations. This diagnostic aid has also been mentioned by Stewart and Illick (37) who have recourse to a barium meal when the powders fail. These authors also use diagnostic pneumoperitoneum and pneumothorax in difficult cases, a procedure they find especially valuable in the presence of tumor masses.

The Trendelenburg position is mentioned by Henri Beclère (6) as very useful in the study of thoracic effusions, of the heart and of mobility of the diaphragm and as an aid in judging the extent of certain cavities.

Empyema pockets may be injected with radiopaque fluids such as

lipiodol and skiagenol and the patient examined in supine, Trendelenburg and lateral decubitus positions to show the extent of the pocket. Matson (28) finds that the injection into pneumothorax pockets with subsequent postural examinations is a distinct aid in differentiating pneumothorax with adhesions from large uncollapsed cavities.

## BIBLIOGRAPHY


(1) Allen, K. D. A., Waltz, H. D., and Hanner, Dorothy D.: A simple method for determining the degree of inspiration from the chest film, Radiol., 1935, *24*, 225.

(2) Allison, Beatrice H.: Special technic for chests, X-ray Technician, 1936, *8*, 71.

(3) Andrus, P. M.: A new method for the radiographic exploration of the mediastinum and concealed portions of the pulmonary fields, Radiol., 1934, *23*, 97.

(4) Banyai, A. L.: Device for the standardization of patient's position in oblique roentgenograms of the chest, Amer. Jour. Roentgen., 1935, *34*, 846.

(5) Baum, F., and Black, Louisa T.: The importance of the apical roentgenogram in pulmonary tuberculosis, Amer. Rev. Tuberc., 1925, *12*, 228.

(6) Beclère, H.: Bull. et Mém. Soc. de Rad. Méd. de France, May, 1932, from the Yearbook of Radiology, 1932, p. 333.

(7) Blady, J., and Cohen, L.: Administration of pneumothorax under fluoroscopic guidance, Radiol., 1935, *25*, 1.

(8) Bowen, Major A.: Quantitative roentgen diagnosis of pleural effusions, Ibid., 1931, *17*, 520.

(9) Brown, S.: Roentgenological examination of the chest in lateral decubitus, Amer. Jour. Roentgen., 1934, *31*, 41.

(10) Dehn, O.: The roentgenologic demonstration of pleural adhesions, Abstract, Ibid., 1935, *34*, 712.

(11) Determann, A.: Advantageous use of filters over parts of roentgenograms, especially in chest exposures, Abstract, Radiol., 1934, *23*, 127.

(12) Ellison, R. T.: Oblique films for the study of adhesions in artificial pneumothorax, Amer. Jour. Roentgen., 1935, *34*, 592.

(13) Exner, F. B., and Rigler, L. G.: The relative value of stereoscopic and single films in the routine examination of the chest, Radiol., 1934, *22*, 236.

(14) Ferguson, J. W.: Roentgen stereoscopy, Amer. Jour. Roentgen., 1936, *35*, 662.

(15) Forestier, J., and Leroux, L.: A simplified method of bronchography, Radiol., 1935, *24*, 743.

(16) Fray, W. W.: The roentgenologic diagnosis of chronic pulmonary emphysema, Amer. Jour. Roentgen., 1934, *32*, 11.

(17) Fray, W. W.: A roentgenological study of pulmonary ventilation: A method for the prediction of normal pulmonary capacities based upon roentgen measurements, Ibid., 1935, *33*, 179.

(18) Fuchs, A. W.: A radiographic view-finder, Radiography & Clinical Photography, 1936, *12*, 1, 2.

(19) Gershon-Cohen, J.: The roentgen examination of the chest. A note on the use of an opaque plastic, Amer. Jour. Roentgen., 1936, *35*, 279.

(20) Greenberg, S.: The superior value of the expiratory roentgenogram in the diagnosis of incomplete pneumothorax, Ibid., 1934, *32*, 330.

(21) Haight, C., and Pierce, C. B.: The evaluation of inter-pleural adhesions by oblique roentgenography, Jour. Thoracic Surg., 1935, *5*, 83.

(22) HAMPTON, A. O., AND KING, D. S.: The middle lobe of the right lung, its roentgen appearance in health and disease, Amer. Jour. Roentgen., 1936, *35*, 721.
(23) JOHNSON, C. R.: Roentgen localization of intrathoracic structures, Amer. Jour. Surg., 1930, *8*, 1237.
(24) JONES, C.: Rib defects simulating pulmonary cavitation, Radiol., 1935, *25*, 533.
(25) KOROL, E.: The lower lung line, Amer. Jour. Roentgen., 1935, *34*, 740.
(26) KOROL, E., AND SCOTT, H. A.: The advantages of the x-ray examination of the chest in lateral recumbency, Radiol., 1933, *21*, 46.
(27) LEVITIN, J., AND BRUNN, H.: A study of the roentgenologic appearance of the lobes of the lung and the interlobar fissures, Radiol., 1935, *25*, 651.
(28) MATSON, R. C.: in GOLDBERG, BENJAMIN: Clinical Tuberculosis, page D 88, F. A. Davis, Philadelphia, 1935.
(29) MATSON, R. C.: Ibid., page D 46.
(30) MATSON, R. W.: Ibid., page D 187.
(31) MEYER, W. H.: Clinical roentgen pathology of thoracic lesions, Lea & Febiger, Philadelphia, 1932.
(32) MILLER, O. O.: Interlobar pleurisy with serous effusions, Kentucky Med. Jour., 1932, *30*, 295.
(33) PANCOAST, H. K., AND PENDERGRASS, E. P.: Jour. Indust., Hygiene, *16*, 165, from the Yearbook of Radiology, 1935.
(34) SAMPSON, H. L.: A double-exposure roentgenological chest technique, Amer. Rev. Tuberc., 1935, *31*, 50.
(35) SANTE, L. R.: The chest, Annals of Roentgenology, vol. *XI*, Paul Hoeber, New York, 1930.
(36) SANTE, L. R.: Manual of radiological technic, Edwards Bros., Ann Arbor, 1934.
(37) STEWART, W. H., AND ILLICK, H. E.: Where is the diaphragm? Radiol., 1934, *22*, 668.
(38) STIVELMAN, B. P.: Interlobar pleural effusions, Amer. Jour. Roentgen., 1935, *34*, 475.
(39) SWEANY, H. C., KEGERREIS, R., AND COOK, C. E.: On intrathoracic localizations by stereoroentgenography, with a consideration of the sources of error, Radiol., 1932, *18*, 277.
(40) THOMAS, H.: A graphic method of recording the respiratory excursion of the diaphragm, Amer. Jour. Roentgen., 1931, *26*, 878.
(41) THOMAS, H.: A shutter grid permitting plural records upon the same film, Ibid., 1932, *28*, 391.
(42) WARFIELD, C. H.: Clinical and roentgenologic value of the lateral chest, Illinois Med. Jour., 1930, *58*, 461.
(43) WATERS, C. A.: Roentgen diagnosis of interlobar pleurisy, In the International Clinics, vol. *2*, 43rd series, p. 194, J. B. Lippincott Co., Philadelphia, 1933.
(44) WESSLER, H., AND JACHES, L.: Clinical roentgenology of diseases of the chest, Southworth Publishing Co., Troy, New York, 1923.
(45) WIESE, E. R.: A simple roentgenographic technic for unilateral density of the chest, Amer. Jour. Roentgen., 1936, *36*, 115.
(46) WILSEY, R. B., AND FUCHS, A. W.: Stereoradiography, Radiography & Clinical Photography, 1932, *8*, 2.
WILSEY, R. B.: The physical foundations of chest roentgenography, Part 1, Amer. Jour. Roentgen., 1933, *30*, 234.
(47) YATER, W. M., AND RODIS, I.: An unusual case of pleural effusion simulating elevation of the diaphragm, Ibid., 1933, *29*. 813.
(48) ZINTHEO, C. J., JR.: A diaphragm and plate divider for chest roentgenography, Radiol., 1934, *23*, 594.

# ROENTGENOGRAPHIC FEATURES OF TUBERCULOSIS IN BONES AND JOINTS[1]

CHARLES G. SUTHERLAND[2] AND ERCELL A. ADDINGTON[3]

Tuberculosis of bones is a metastatic (secondary) process, resulting from the implantation of the tubercle bacillus, or more commonly, from the lodging of an embolus of tubercle bacilli, in that portion of a bone which offers the most favorable conditions for the development of the bacilli. The generally accepted opinion is that the primary tuberculous infection results from the inhalation of droplets of infected sputum, disseminated by persons suffering from open pulmonary tuberculosis, or that the infection results from the ingestion of tubercle bacilli in the milk of tuberculous cattle. The greatest number of primary tuberculous infections occur among infants and children and are situated in the lungs. Infection may occur in the intestines, in the skin of the genitals as a result of ritual circumcision, in the middle ear, in the parotid gland, in the nose, in the conjunctiva or in the tonsils, but such occurrences are comparatively rare. Congenital infection cannot be disproved, but it is so rare that it may be dismissed as having no practical application. Harris (8) thought that infection of bone from a primary focus in the tonsil was more frequent than is generally appreciated.

One needs but to mention the following sequence of events in the development of the pulmonary lesion: the implantation of the tubercle bacillus, the formation of the tubercle and the primary allergic reaction about it which results in a bronchopneumonic focus. Coincidently with, or immediately following the development of the pulmonic infection, occurs the involvement of the regional lymph nodes through centripetal conveyance of the infection by the lymphatics, the two processes together constituting the primary complex. Patients who have tuberculosis of bone probably are those who have survived the various stages of the primary infection; in the majority of cases the lymph nodes remain

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] The Mayo Clinic, Rochester, Minnesota.

[3] Fellow in Radiology, The Mayo Foundation, Rochester, Minnesota.

as the sole indicator of the healed primary complex (Ghon) which is difficult to recognize; a proportion of the patients show evidence of secondary pulmonary infection (adult pulmonary tuberculosis), a few have active tuberculosis, but the majority have healed tuberculosis.

Apparently, much the same sequence occurs when the primary focus is elsewhere than in the lung, because the end result is always mediastinal adenitis when the infection occurred by the aerogenous route, or a mesenteric adenitis when the infection occurred by the enteric route, or a cervical adenitis when the infection occurred by way of the pharynx, or some other form of regional adenitis when the infection was cutaneous.

Investigation has proved that encapsulation of tubercle bacilli, even by calcification, does not kill them, and also that the bacilli may remain for a long time in the tissues without producing gross or even microscopical changes. When the equilibrium between the immunity caused by the primary tuberculous infection and the natural resistance of the individual is disturbed as a result of any known or unknown cause, often as a sequel to some intercurrent infection, bacilli can become mobilized and cause secondary lesions.

The situation of the lesion in tuberculosis of bone is related to the architecture of the circulatory system. The tubercle bacilli reach the blood-stream by means of the thoracic duct, or by rupture of a caseating mass in a tuberculous lymph node, or of a tuberculous area in the lung into a blood vessel. In the great majority of cases the bacilli are effectively disposed of, but occasionally a bacillus, or a group of bacilli, reaches some distant organ or part of the skeletal system where between two sources of blood supply there is a slowing of the current favoring stasis and lodgment of this infectious material. Kolodny (9) reviewed the various theories supporting this haematogenous method of secondary infection and presented the results of his own investigations. He believed that the anatomical facts spoke in a simple and positive way for the embolic theory of the pathogenesis of tuberculosis of bone. Ely (4) pointed out that all through the body the lymphoid tissues were the great feeding ground for the tubercle bacillus. Tuberculosis, for this reason, was found in the spongy ends of the long bones, where the marrow was of the lymphoid variety; it was not found in the short and flat bones throughout the body. Except in young children, the marrow in the shaft consists of little else than fat, which is a poor culture medium for the tubercle bacillus. The presence of the lymphoid marrow in the region of the joint seems to depend, at least in the adult, largely on

the presence of function in the joint. The presence of the synovial membrane depends absolutely on the presence of function in the joint. Nature's whole protective reaction is in the direction of depriving the joint of function, in other words, of destroying it. Ely considered that the end result of treatment, such as immobilization in the case of children, and heliotherapy, passive congestion, and so forth as auxiliary measures, and complete and permanent destruction of the joint and avoidance of secondary infection in the adult, was efficient proof of his theory. The disease may start in either the lymphoid marrow or in the synovial membrane, and later may involve either of these structures, or it may remain indefinitely in one of them alone. If it remains in the marrow and does not involve the synovial membrane, it is, strictly speaking, not a tuberculous arthritis but simply a tuberculous osteomyelitis, but if it ever attains sufficient importance to cause clinical symptoms it almost invariably involves the joint.

Greig (7) found that secondary involvement of the bone was commonly epiphyseal, in contrast to the invariable occurrence of the acute septic process at the metaphysis (the spongy end piece of the diaphysis that borders on the epiphysis). He considered tuberculosis of bone as essentially a disease of childhood and adolescence, although it might become manifest at any age and even in senility. In older persons it can often be proved to be a recrudescence of an affection that had remained latent even during many years.

The outstanding roentgenographic characteristic of tuberculosis of bone is the translucency of the bony shadow without evidence of proliferation of bone (reaction). Greig wrote:

When the tuberculous affection begins in the diaphysis it may be periosteal but more frequently is endosteal or medullary. Of the long bones the tibia is probably the most commonly affected. The process by which the portion of a diaphysis affected with tuberculosis changes from its normal shape to a thin-walled fusiform expansion is not generally appreciated. There seems to be an idea that the bone is distended by pressure of the tubercles from within. As bone is a rigid structure such a supposition is manifestly absurd. The presence of tubercles, their bacilli and their toxins within the marrow cavity or within the haversian canals or even on the surface, acts as a foreign body and as such provokes a histamin-induced hyperemia. When the hyperemia reaches a certain degree, a consequent decalcification follows with proliferation of fibroblasts. The bone becomes soft and the softened tube now re-accommodates itself to its contents and with this relief the hyperemia diminishes and at once

the local excess of calcium is utilized to form new bone. With the variation of intensity of the hyperemia, decalcification and recalcification alternate, yet proceed synchronously, throughout the affected part, and the gradual readjustment which takes place is greater at the middle than at the extremities of the affected portion and so continues until, it may be, the whole diaphysis participates. A sequestrum is not common in tuberculous disease because of the increase of peripheral hyperemia which the tubercle provokes and of the degree of periosteal hyperemia which it excites. Hyperemia is essentially a decalcifying agent. The tuberculous process commencing within the marrow cavity, the zone of increased vascularity around the disease rapidly decalcifies the cancellous bone. Should minute spicules or fragments of the trabeculae escape decalcification they may find their way into an avascular purulent or caseous area of fused tubercles where they remain as fine gritty particles. In some forms of infiltrating tuberculous osteomyelitis, however, larger areas of bone may be more or less isolated, and in the short long bones the whole body of the bone may be thus affected. Even then the so-called necrotic bone lies in a mass of tuberculous granulation tissue and in virtue of the granulation tissue is undergoing rapid decalcification. It never forms a true sequestrum, a dead homogeneous entity, unless sepsis be superadded. In the absence of sepsis any dead osseous tissue will be effectively dealt with by the inflammatory process and will ultimately disappear, its decalcification providing an immense amount of local excess of calcium which goes to form the light porous fusiform involucrum standing well away from the necrotic shaft, so characteristic of tuberculous dactylitis. Subperiosteal, serous edematous effusion takes place and raises the periosteum from the bone (more easily in the middle than at either extremity) ensuring the fusiform shape so frequently found in tuberculous phalanges, metacarpal and metatarsal. As the periosteum reaches the limit of its expansion, the stretching diminishes its vascularity and the great local excess of calcium is again available for the formation of bone. The new bone is nodular and porous and forms a cylindrical or fusiform sheath enclosing the remains of the original body of the bone in which decalcification is preceding obliteration. This sheath is at the periosteum because there, and there only, in the diseased bone can there be the necessary combination of adequate blood supply and excess of calcium salts, but it is not formed by the periosteum. That new bone is subperiosteal does not mean that it is periosteal in origin. In children the tuberculous process seems to be more rapid and acute, doubtless the hyperemia is more intense and possibly suppuration more readily occurs, and so the formation of cloacae and sinuses from the superadded septic infection. A leash of vessels, comparable to the pannus of the cornea, and not inaptly termed "articular pannus" is a common feature on the cartilaginous surfaces of the tuberculous joint. This is a vascular intrusion with very few fibroblasts which precedes the tubercle and which in virtue of its hyperemia

prepares by liquefaction and destruction of the cartilages, the way for the tuberculous extension (not exactly tuberculous granulation). And so under the cartilages the tubercles can only spread after a vascular intrusion has decalcified the bone and softened the overlying cartilage. But the dedifferentiation of cartilage is slower than the decalcification of bone, and so the encrusting cartilage is isolated as flakes and masses lying in the vascular zone which has decalcified the bone and which will in time destroy the cartilage. As long as hyperemia is great, new bone is not formed nor does ankylosis take place. But in time the hyperemia diminishes, partly from endarteritis narrowing the vessels and partly from perivascular fibrosis and then the local accumulation of calcium is utilized, the surface becomes nodular, ankylosis takes place and the tuberculous arthritis has undergone "spontaneous cure." Toxic endarteritis of tuberculosis is a late affection. In tuberculosis and sepsis, a periarterial fibrosis is an important local adjunct and indeed may be the chief determinant.

Phemister (11) in 1924 made some interesting observations on the effect of pressure on articular surfaces in pyogenic and tuberculous arthritis. These were summarized in a second communication in 1933 (12). Whether the metastatic implant was in the bone or in the synovial membrane, a diffuse tuberculous synovitis eventually developed and the pannus attacked the cartilage. In some joints the articular cartilages fit accurately together, while in others, particularly the knee, they are of different contour, so that there are large areas of both free and contacting surfaces. In joints in which the articular surfaces are extensively in contact (for example, the hip and ankle) the action of the pannus is restricted but the surfaces of the cartilage are destroyed to some extent by erosion at the margins. In joints in which there are both free and contacting surfaces of cartilage, the free cartilage is gradually eroded. As the disease progresses, the articular cartilages suffer from nutritional disturbances and from the action of the pannus. The persistence of the loosened cartilage was attributed for a long time to the absence of proteolytic ferments in tuberculous exudate. At this stage the roentgenological characteristics in the hip and ankle are regional atrophy of bone, reduction of or loss of density of the shadow of the bony articular cortex, and the preservation of the normal width of the cartilage space of the joint. In the knee, because the entire thickness of cartilage and underlying cortex of the bone in a part or the whole of involved regions may be destroyed, the roentgenographic image would show regional atrophy of bone, diminution of or loss of the shadow of the bony articular surface in the noncontacting regions and preservation

of the shadow of the bony articular cortex and of the cartilaginous space in the contacting regions of condyles and tuberosities. Eventually, the entire articular cartilages may be destroyed. This will result in a narrowing or complete loss of the intercartilaginous space of the joint. In the advanced stages, the bone may be secondarily invaded at the traumatized points of contact and weight-bearing will result in large areas of necrosis. The invasion is usually bilateral at opposite points in the bone; after a long time detached areas result in kissing sequestra. The roentgenological characteristics of regions of secondary invasion and necrosis of bone are more or less conical or hemispherical shadows of bone bordering on the weight-bearing portion of the joint, with an incomplete line of demarcation about it, and usually there is a shadow that is denser than the surrounding living bone. Usually, the shadow of the bony articular cortex of normal or reduced density is preserved and the condition is bilateral, which produces the picture of kissing sequestra. In some instances the dead bone is completely destroyed, and pits and grooves are left along the articular surfaces. An original focus in the bone bordering on the joint, if small, may break down and leave a pit or cavity. A large focus becomes separated as a sequestrum and retains its original density.

In tuberculous arthritis of young children the pathological changes vary somewhat from those in tuberculous arthritis of adults. In the larger joints, and in particular the knee, where there are relatively thick articular cartilages, destruction of the noncontacting portions is less complete in children than it is in adults. The articular cartilage is not frequently detached and left free in the joint. In the smaller joints with thinner cartilages and in older children, the course is more nearly like that in adults. Partitioning of the knee joint by healing processes occurs oftener, and different degrees of involvement within the partitions are more pronounced in children. The original focus in bone that can definitely be identified, either by the roentgen rays or at operation, is more frequently situated in the metaphysis than in the epiphysis. Secondary invasion of bone is usually bilateral in the joint and is most marked at the points of weight-bearing much as it is in adults, but it usually results in destruction rather than sequestration of the necrotic bone, regardless of the extent of the involvement.

Kolodny compiled 35,000 cases of tuberculosis of bone and joint from the literature and found the percentage of incidences to be: vertebral column, 39.1, hip 31.4, knee 15.0, and wrist 1.7. He found a similar

parallelism between the frequency with which certain skeletal regions were affected and their blood supply. In the shoulder the implantation was usually found in and about the *sulcus bicipitus humeri*, and the process extended to the medial aspect of the head, to the *tuberculum majus humeri* and even to the diaphysis. The infectious focus in tuberculosis of the knee in children was situated in the epiphysis of the femur in 59 per cent, in the epiphysis of the tibia in 34 per cent, and in the patella in 7 per cent of cases. The lateral epicondyle of the femur was the most frequent site, the medial condyle next, and the intercondyloid notch was the least frequent site of infection. The first evidence of tuberculous involvement of the hip joint was in the synovial membranes in adults and in the bones in children. Kolodny found that it was in the acetabulum in 57 per cent, in the head of the femur in 25 per cent, and in the neck of the femur in 18 per cent of cases. The most frequent site of commencement of synovial tuberculosis was the *fossa acetabuli*, the origin of the *ligamentum teres femoris*, while tuberculosis of bone originated about the middle of the Y-shaped cartilage.

In a necessarily brief review of this subject we have been able to present only the outstanding features by which the roentgenographic image, which is in fact a reproduction in relief of the normal and the abnormal tissue structures, can be recognized. A bibliography is appended which includes data on the less commonly observed types of tuberculous involvement of the skull, the clavicles, the trochanters, the femur and the ribs. Tuberculosis of the spinal column was not included in this study because of the limitations of time and space. *Osteitis tuberculosa multiplex cystica* is most frequently associated with cutaneous tuberculosis; in other reported cases there would seem to be some doubt as to the classification. Greenwood (6) found tuberculosis of the ankle joint so subtle in onset that, as a rule, little could be ascertained about its true genesis. Beginning usually in the astragulus or *os calcis*, less frequently in the cuboid, the disease is often overlooked at its inception.

In general, rarefaction with little or no evidence of reaction of tissues and a clouding of any joint due to effusion should at least arouse a suspicion of tuberculosis as the aetiological factor.

## REFERENCES

(1) Brailsford, J. F.: The radiology of bones and joints, Baltimore, William Wood and Co., 1934, 500 pp.

(2) Bromer, R. S., and Downs, E. E.: Tuberculosis of the diaphysis, Amer. Jour. Roentgenol. & Radium Therap., 1933, *29*, 617.
(3) Elliott, A. E.: Tuberculous cysts of the knee joint, Ibid., 1935, *34*, 209.
(4) Ely, L. W.: The treatment of joint tuberculosis, Amer. Jour. Surg., 1921, *35*, 261.
(5) Ghormley, R. K.: Tuberculosis of bones and joints, in Nelson New Loose-Leaf Surgery, New York, Thomas Nelson and Sons, chapt. 1, vol. *3*, 1934, pp. 15–46.
(6) Greenwood, H. H.: The relation of tuberculosis to Köhler's disease, Brit. Jour. Surg., 1927, *15*, 245.
(7) Greig, D. M.: Clinical observations on the surgical pathology of bone: tuberculosis of bone, Edinburgh, Oliver and Boyd, chapt. 4, 1931, pp. 72–93.
(8) Harris, R. I.: Observations on the pathology of surgical tuberculosis: with particular reference to the incidence of tuberculous bacilluria, Amer. Jour. Surg., 1930, *10*, 514.
(9) Kolodny, A.: A contribution to the knowledge of pathogenesis of skeletal tuberculosis, Jour. Bone & Joint Surg., 1925, *23*, 53.
(10) Meyerding, H. W., and Mroz, R. J.: Tuberculosis of the greater trochanter, Jour. Amer. Med. Assn., 1933, *101*, 1308.
(11) Phemister, D. B.: The effect of pressure on articular surfaces in pyogenic and tuberculous arthritides and its bearing on treatment, Ann. Surg., 1924, *80*, 481.
(12) Phemister, D. B., and Hatcher, C. H.: Correlation of pathological and roentgenological findings in the diagnosis of tuberculous arthritis, Amer. Jour. Roentgenol. & Radium Therap., 1933, *29*, 736.
(13) Sanes, S., and Smith, W. S.: Osteitis tuberculosa multiplex cystica of fibula and tibia, Jour. Amer. Med. Assn., 1934, *102*, 1206.
(14) Schwentker, F. F.: Cystic tuberculosis of the bone, Amer. Jour. Dis. Child., 1931, *42*, 102.
(15) Sirkin, J., and Baumgartner, E. A.: Tuberculosis of the clavicle: review of the literature and report of a case, Jour. Amer. Med. Assn., 1936, *107*, 120.
(16) Straus, D. C.: Tuberculosis of the flat bones of the vault of the skull, Surg., Gynec. & Obst., 1933, *57*, 384.
(17) Van Alstyne, G. S., and Gowen, G. H.: Osteitis tuberculosa multiplex cystica (Jüngling) report of case involving larger long bones with complete proof of its tuberculous etiology. Review of literature, Jour. Bone & Joint Surg., 1933, *15*, 193.
(18) Van Antwerp, L. D.: A case of tuberculosis of the humeral diaphysis and the cranial vault, Amer. Jour. Roentgenol. & Radium Therap., 1935, *34*, 50.
(19) Vastine, J. H., and Bacon, Emily P.: Osteitis tuberculosa multiplex cystica, Radiol., 1935, *24*, 22.

# HERNIA OF THE LUNG[1,2]

## Intercostal, Cervical and Mediastinal

EPHRAIM KOROL[3]

*Definition:* Hernia of the lung is a protrusion of the lung and its pleural membranes either through the chest-wall outward or through the mediastinal septum into the opposite hemithorax.

Hernia is to be distinguished from prolapse of the lung. In the latter condition, the parietal pleura is ruptured and there is no hernial sac.

*Classification:* Until now, lung hernias have been classified, according to location, into cervical, intercostal, and diaphragmatic hernias. Mediastinal lung hernias have heretofore not been given recognition, at least they are not included in the classification, and I find but one case of this form of hernia described in the literature (1). However, this is the most common form of lung hernia and is increasing in frequency with the practice of artificial pneumothorax. After pneumothorax refills are discontinued and the treated lung fails to expand, the pressure is very low on the treated side; the opposite lung is then gradually drawn across the midline through certain localized "weak spots" in the mediastinal septum. The recently introduced operations of lobectomy and pneumonectomy are also destined to increase the incidence of this form of hernia.

I, therefore, propose that mediastinal lung hernia be included in the general classification of lung hernias. On the other hand, there seems no reason to retain the classification of diaphragmatic lung hernia. The literature does not contain a single case of diaphragmatic lung hernia, that is, a protrusion of the lung and its intact serous membranes into the abdominal cavity. The oft quoted case of Beale (2) upon examination proves to be a case of lung prolapse rather than hernia. A consideration of the pressure relations involved indicates that in all cases

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] Published with the permission of the Medical Director of the Veterans Administration who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

[3] Veterans Administration Facility, Lincoln, Nebraska.

of congenital or acquired defects of the diaphragm, herniation can occur only from the abdomen into the chest and not from the chest into the abdomen.

*Pathogenesis:* As in all other hernias, the bulging takes place either through a preformed or newly formed channel in the chest-wall or mediastinum. The preformed channels are: (*1*) the apical aperture of the chest; (*2*) the anterior mediastinal weak spot, the space between the sternum and the heart at the site of the atrophied thymus gland; and (*3*) the posterior mediastinal recesses between the oesophagus and the aorta below the level of the trachea and the arch of the azygos vein.

The anterior interpleural space is normally occupied by fatty and loose areolar tissue which offers little resistance to displacement by increased intrathoracic contents on one side or decreased contents on the opposite side. The anterior mediastinal septum may bulge outward and may come to rest in the axilla, allowing the upper lobe of the invading lung to occupy the entire anterior aspect of the opposite chest. In such cases an attempt to induce a pneumothorax on the contracted side of the chest may result in a collapse of the opposite lung, the needle entering the pleural cavity of the herniated lung. One such case, abundantly illustrated, was reported by Derscheid and Toussaint (3). An attempt to collapse the left lung resulted in a pneumothorax on the right side and no pneumothorax on the left. The roentgenogram shows the left lung greatly contracted, while the right lung had hypertrophied and invaded the left side in the form of a hemispherical bulging, which nearly touches the left lateral chest-wall. Lipiodol injected through the left axilla is seen to flow into the right side of the chest.

This curious complication of artificial pneumothorax, that is, the production of an unintentional pneumothorax on the contralateral side, was reported by several other writers (4, 5, 6, 7), and was generally interpreted as due to an interpleural fistula. In the one case that was examined postmortem, no such fistula was found (4). I reviewed all these cases and I am convinced that no interpleural communication was present in any of these cases. In all of them there was clear X-ray evidence of mediastinal lung hernia. The operator's needle introduced on one side of the chest entered the pleural cavity of the opposite lung; as a result, the pneumothorax was produced not on the desired side but on the opposite side.

In the posterior mediastinum the oesophagus is the only organ which runs the entire length of the chest and which sends no branches to other

structures; it is, therefore, easily displaced by pressure changes. In the cervical region the oesophagus follows the trachea in all conditions which cause deviation of the trachea. In case one lung apex is contracted, the trachea moves forward and to the contracted side, accompanied by the oesophagus. The opposite apex hypertrophies and crosses over the spine back of the oesophagus. This deviation of the trachea is familiar but the accompanying forward and lateral movement of the oesophagus is not well known. It can be easily demonstrated by appropriate X-ray examination. In the routine chest films the inner border of the enlarged lung apex can be seen in the opposite hemithorax.

The oesophagus is most easily displaced in the lower part of the chest where it normally parts company with the aorta and turns forward and to the left to reach the stomach. Any bulging of the lung or mediastinal pleura will invade the opposite hemithorax in this space between the oesophagus and aorta. The lower lobe of the invading lung may come to fill the entire posterior aspect of the opposite side of the chest.

Roentgenograms and drawings from anatomical specimens of such cases can be seen in recent papers by Rienhoff (8) and by Beutel and Strand (9). Nitch's paper (10), dealing with the mediastinal "weak spots," contains photographs of anatomical preparations. Nitch was interested not in lung hernia but in balloonings of the mediastinal pleura in tension pneumothorax; the anatomical factors which determine the site of the herniation are the same in both conditions.

In this connection, I wish to confirm Rienhoff's observation that the right lung can invade the opposite hemithorax to a greater extent than the left lung. This difference is largely due to the direction and attachment of the oesophagus and to its relation to the mediastinal pleura. Anterior mediastinal lung hernias are as common on the right as on the left side, but the posterior mediastinal bulging is hardly ever seen on the right side. The oesophagus undergoes relaxation in its leftward displacement, but it becomes stretched and resists rightward displacement, due to its diaphragmatic attachment on the left side. The relations of the mediastinal pleura are normally different on the two sides (11), the right pleura extending posterior to the oesophagus, forming a recess behind it from the tracheal bifurcation down to the diaphragm. The left pleura is not in direct contact with the oesophagus. It is thus easier for the right lung to invaginate itself between the aorta and the oesophagus than it is for the left lung.

The lung apex, as is well known, is less protected by bone and muscle

than the other parts of the lung, and it normally bulges out of its boundaries during expiratory efforts made with closed glottis. In exceptional cases, generally in association with pulmonary emphysema and chronic cough, the bulging may gradually increase in size and it may become permanent. The location of the hernia is in front of the neck on one side of the larynx. However, malformations in the region of the thoracic inlet are very uncommon. The anomalies consist of accessory ribs or muscles, such as cervical rib and scalenus minimus muscle, which tend to strengthen rather than to weaken the chest-wall. For this reason, the cervical hernia is the most uncommon form of lung hernia. I have not seen it in my practice, and I encountered only some twenty case reports in an extensive review of the literature. A drawing of an anatomical specimen can be seen in Cockle's (12) paper; roentgenograms are shown by Otonello (13) and by Graham (14). Graham also shows photographs of the patient, as well as a surgical dissection of the hernia.

The intercostal lung hernia usually occurs in the front of the chest, internal to the costochondral junctions of the ribs. The intercostal musculature is thinnest in this region, the external intercostal muscles being absent altogether. Malformations of the ribs and muscle anomalies, which weaken the chest-wall, also, by preference, involve the front of the chest. I came across but one report of a nontraumatic hernia which pointed on the posterior chest-wall (15); in an infant, with cystic emphysema of the lung, one of the cysts bulged along the tract of an intercostal vessel in the left fourth interspace posteriorly.

There are numerous cases in the literature, showing the association of malformation of the ribs and atrophy of the pectoral muscles with lung hernia (16, 17, 18, 19). The majority of the writers ascribed the hernia to the weakened chest-wall; others held that the protruding lung caused the rib erosion (20) and the muscle atrophy (21). Caries of the ribs (22) and intercostal neuritis (23) have also been given as aetiological factors.

The most common form of intercostal hernia is the traumatic variety which follows surgical or accidental injuries to the chest-wall. In a previous study, I had the occasion to show photographs of a patient and chest roentgenograms of traumatic hernia (24).

*Symptoms and signs:* In the external hernias, there is a tender swelling which increases on exertion and on coughing. The overlying skin is normal in color and freely movable. The swelling has a typical air-cushion feel. On manipulation, the swelling can be reduced, often with

a gurgling noise. On careful palpation, the neck of the hernia can be made out, as well as the orifice in the chest-wall, through which the hernia can be reduced. The percussion note is hyperresonant and the breath-sounds are harsher than over the neighboring chest-wall. On the roentgenogram the hernia shows in the form of a circular area of increased translucency, at first glance suggesting a tuberculous cavity; in the oblique view the hernia can be shown outside of the chest-wall (figure 1B).

The mediastinal lung hernia gives no symptoms, and the physical signs are few. In cases of marked asymmetry of the chest caused by fibrosis or atelectasis of one lung, one may look for signs of mediastinal hernia. The hyperresonant percussion note of the emphysematous lung may extend across the midline between the first and third ribs anteriorly and at the base of the lung posteriorly. Auscultation generally gives no clue as the herniating lung is emphysematous and the breath-sounds are feeble over the hernia, as well as over the contiguous lung.

The X-ray appearance is characteristic. The large hyperaerated lung is seen to extend into the opposite side in the form of one or two bulgings, having well defined convex outer borders. The upper bulge which can be shown to be anterior by fluoroscopic examination, reaches from the first to the fourth rib. The lower bulge extends from the level of the fifth or sixth dorsal vertebra to the diaphragm. The trachea is displaced to the contracted side. Closer examination of the tracheal lumen will often show that the apex of the hypertrophied lung has also extended into the contracted hemithorax and its outer border can be seen through the tracheal transparency at a considerable distance from the midspine.

Examination of the oesophagus with the aid of a barium mixture will show its displacement as described in a preceding paragraph.

Mediastinal lung hernia may be considered a rather common condition and I believe it unnecessary to cite many case reports. I had the opportunity on previous occasions to show a case of herniation of the right lung in atelectasis of the left lung (25); also a case of herniation of the left lung in right fibrothorax (26).

One reason for the tardy recognition of this form of hernia is the fact that during postmortem opening of the chest, the herniating lung collapses and the hernia becomes inconspicuous.

## CASE REPORTS

*1:* World War veteran, age 49. In January, 1936, he was convalescing from an alcoholic debauch and was rather slow in regaining his strength and his body weight. There was an annoying morning cough and some fever. There was a painful area above the right breast which would swell up every morning during the coughing spells. He was admitted to the hospital on March 20, 1936, with a diagnosis of unresolved pneumonia. The next morning the man complained of soreness about the right breast. Examination disclosed a hemispherical bulging in the chest-wall between the right clavicle and the nipple. The overlying skin was tense but not discolored. The swelling felt spongy and at several points air crepitus was felt. There was hyperresonance on percussion and the breath-sounds were exaggerated over this area. Upon manipulation the swelling collapsed rather suddenly with an audible gurgle. Beneath the clavicle in the parasternal line, there was a defect in the chest-wall; pressure with the finger at this point would prevent the reduction of the mass. Upon removal of the pressure, the hernia was felt to disappear into the chest through this opening.

Roentgenological examination on March 26, 1936, resulted in the following report by Dr. Harry A. Scott: "There is now an irregular annular shadow seen between the levels of the 1st and 3rd ribs near their anterior ends. Observation under the fluoroscope shows that there is a herniation of the lung through the anterior chest wall at the level of the 2nd rib; the air is seen just beneath the skin in this region. The area of herniation is 6 cm. in diameter. The films also show a defect in the anterior end of the 2nd rib on the right side." (Figure 1A.)

There was no history or signs of any injury to the chest-wall. The hernia developed insidiously and it was first noticed a few days before his admission to the hospital. The man later showed symptoms and signs of acute endocarditis and he died on April 22, 1936.

---

FIG. 1A. Case 1. Intercostal hernia of right lung producing annular area of increased transparency between the clavicle and third rib. The arrow points to the neck of the hernial sac. (See text.)

FIG. 1B. Case 1. Oblique view. Part of the hernia visible outside of the chest-wall. Arrows point to hernial canal.

FIG. 2. Case 2. Mediastinal hernia of left lung in a case of fibroid tuberculosis of right lung. Postmortem confirmation. (See text.)

FIG. 3A. Mediastinal hernia of right lung in case of atelectasis of left upper lobe. Film taken in expiration, as the hernia was more conspicuous in this phase of respiration.

FIG. 3B. Lateral view of same case. Barium in oesophagus. Note the displacement of oesophagus from the spinal column.

FIG. 4. Anterior (upper arrow) and posterior mediastinal lung hernias. Barium in the oesophagus.

FIG. 1A

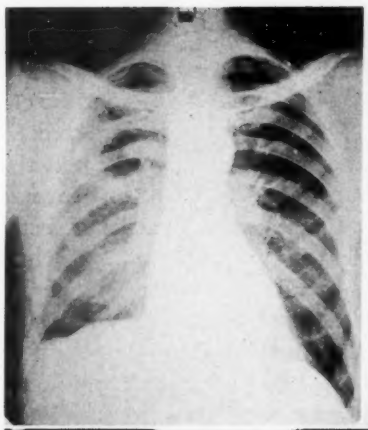
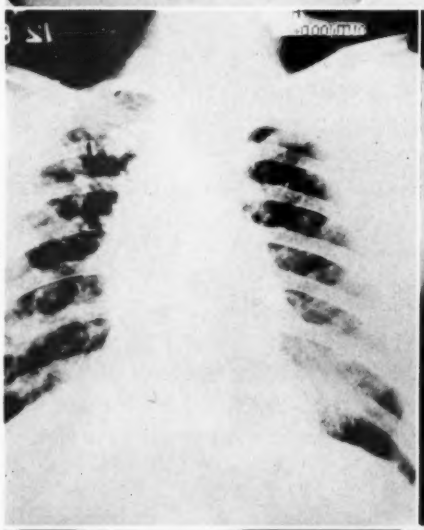


FIG. 1B

FIG. 2



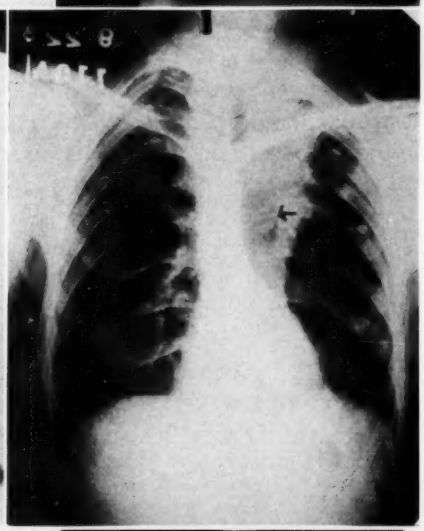


FIG. 3A

FIG. 3B

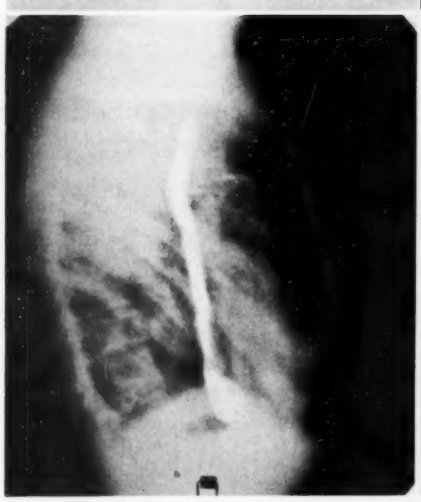


FIG. 4

The hernia was reduced at the time of death. Following is an excerpt of Dr. Harry A. Scott's autopsy protocol: "A portion of the 2nd rib, about 2.5 cm. in length, is missing near the anterior end. The ends of the ribs are smooth. Upon opening this area from the outside, a pocket is revealed which, at this time, contains only air. The pocket measures about 4.5 cm. in diameter. It extends anterior to the 2nd rib, also above and below it just beneath the muscle layers. The posterior wall is formed by the parietal pleura. The lung is firmly adherent to the chest wall around this area; upon section, it is found to be emphysematous in the neighborhood of these adhesions."

In a middle-aged man who was in poor health, there developed an intercostal hernia, following an attack of pneumonia. There was malformation of the second rib and the adjacent herniating lung was emphysematous.

*2:* This World War veteran had been known to have fibroid tuberculosis of the right lung since the spring of 1921. He was treated at the U. S. Veterans Hospital, Outwood, Kentucky, for nearly two years in 1934 and 1935. The physical signs recorded were: "Limited expansion of the right chest; whispered pectoriloquy and amphoric breathing over the upper part of the right chest with medium moist râles. On the left side the breath sounds were compensatory over the upper lobe and the expiration was prolonged. The series of X-ray films showed progressive contraction of the right lung with displacement of the mediastinum to the right. On the film of December 5, 1932, there is a semilunar area of increased transparency with convex outer border projecting from the mediastinum into the right lung opposite the first and second anterior interspaces (figure 2). The film dated August 11, 1933, shows the contraction of the right lung and the opacity of the right base to be more pronounced. The area of increased transparency is larger; it nearly reaches the lateral chest wall."

The patient died of tuberculous meningitis.

Following is an abstract of the postmortem report made by Dr. E. J. Butzke on June 23, 1935: "The left lung is large, extending across the upper third of the chest to the right about three and one-half inches. The mediastinum and heart are displaced considerably to the right. The left lung is removed easily. It is light in weight and emphysematous. The right lung is only one-third its normal size. It is adherent to the parietal pleura and cannot be removed. It shows dense adhesions to the mediastinum and there are numerous cavities."

In a case of fibroid tuberculosis, the right lung underwent marked contraction. The left lung invaded the right hemithorax and the left upper lobe filled the front of the right chest.

SUMMARY

1. Lung hernia is to be distinguished from lung prolapse and from the pleural bulgings seen in tension pneumothorax. In lung prolapse there is no hernial sac; in pleural hernia there is no lung tissue.

2. Lung hernias depend on an increased thoracic content, usually emphysema, coupled with congenital or acquired defects in the chest-wall. Coughing or straining efforts are the precipitating cause, as in inguinal hernias. Like the inguinal hernia, the lung hernias enlarge in expiration.

3. The intercostal lung hernias are associated with malformation of the chest-wall, and with atrophy of the pectoral or intercostal muscles. The cervical hernias are the least common of the lung hernias, due to the rarity of malformation of the clavicle.

4. The mediastinal hernia is the commonest form of lung hernia. It is brought about by emphysema of one lung associated with contraction, atelectasis or absence of the opposite lung. Mediastinal lung hernia is accompanied by displacement of the mediastinum *in toto*. However, certain regions in the mediastinum deviate more than others, allowing the lung to be displaced into the opposite hemithorax beyond the lateral boundaries of the mediastinal septum.

5. The current classification of lung hernias is to be modified by leaving out diaphragmatic lung hernia and by adding mediastinal lung hernia.

The author expresses indebtedness to Dr. Charles M. Griffith, Medical Director, and Dr. Philip B. Matz, Chief of the Research Subdivision of the Veterans Administration, for encouragement in this work, and for the gathering of material and case records for this and other studies from the several facilities of the Veterans Administration.

REFERENCES

(1) Urizio, L.: Di un'ernia mediastinica anterosuperiore, Riv. di pat. e clin. d. tuberc., 1931, *5*, 773.

(2) Beale, C.: Case of hernia of the lung through the diaphragm, The Lancet, January 28, 1882.

(3) Derscheid, G., and Toussaint, P.: Pneumothorax artificiel droit par implantation d'une aiguille dans l'aisselle gauche, Arch. Med.-Chir. App. Resp., 1932, *7*, 68.

(4) Smith, C. R., and Willis, M. S.: Communication between the two pleural sacs, Jour. Amer. Med. Assn., 1933, *101*, 16.

(5) Johanson, L., and Prozorov, A.: A case of intercommunicating pleural cavities, Borba s Tuberk., 1932, *10*, 172.

(6) Jullien, W.: Communications interpleurales observées au cours de l'applications du pneumothorax artificiel, Jour. Méd. Français, 1930, *19*, 392.

(7) Dumarest and Marinet: Bull. Méd. de la Station d'Hauteville-Lampe, October, 1929.

(8) RIENHOFF, W. F.: Intrathoracic readjustments following complete ablation of one lung, Jour. Thoracic Surg., 1937, *6*, 254.
(9) BEUTEL, A., AND STRAND, F.: Zur bronchographischen Diagnostik des angeborenen Lungenmangels, Fortsch. Roentgenstr., 1937, *54*, 49.
(10) NITCH, G.: Die schwachen Stellen des Mediastinums, Beitr. Klin. Tuberk., 1910, *18*, 1.
(11) CUNNINGHAM, D. J.: Textbook of anatomy, ed. 3, 1909, p. 1040.
(12) COCKLE, J.: Contribution to the pathology of tumors of the neck, Med. Times & Gazette, January 4, 1873.
(13) OTONELLO, P.: Un caso raro di ernia polmonare dell' apice destro, Radiologia Medica, 1931, *18*, 1054.
(14) GRAHAM, E. A.: Hernia of the lung and adenoma of thyroid, Surg. Clinics of North America, 1922, vol. *2*, p. 1493.
(15) FRUEWALD, F.: Hernia Pulmonalis aus blasigen Lungenmissbildungen, Jahrb. f. Kinderheilk. und Physische Erziehung, 1885, vol. *23*, p. 418.
(16) LEREBULLET, P., BOIZE, P., AND ODINET, J.: Hernia congénitale du poumon liée a une malformation complexe de la paroi thoracique, Bull. Soc. Pediatrique, Paris, 1933, *31*, 231.
(17) DREIFUSS, A.: Ein Fall von congenitaler Lungenhernie, Deutsch. Zeitsch. f. Chirurgie, 1924, *187–188*, 274.
(18) POLYA: Congenitaler Defect der Brustmuskeln mit Lungenhernie, Pester Med. Chir., 1909, *45*, 149.
(19) LITTLE, R. R.: Congenital defect of the pectoral muscles, New England Jour. Med., 1936, *264*, 934.
(20) HOCHSINGER: Lungernhernie im ersten Kindesalter, Wien. Med. Wchnschr., 1888, no. 39.
(21) CHAVANNEZ: Un cas de pneumocele spontanément reducible, Jour. de Méd. de Bordeaux, 1893, *23*, 237.
(22) DUNCKER, F.: Lungenhernie bei Spondylitis tuberkulosa, Arch. f. Orthopaedie, Mechanotherapie, und Unfallschieurgie, 1913–14, *13*, 140.
(23) GERMER: Ein neuer Fall von traumatischer Lungenhernie ohne penetrierende Thoraxverletzung, Münch. Med. Wchnschr., 1906, *53*, 1810.
(24) KOROL, E.: Paradoxical breathing, Arch. Int. Med., 1933, *51*, 264.
(25) KOROL, E.: Atelectasis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1931, *23*, 500.
(26) KOROL, E.: The operation of Pascal's Principle in the lungs and pleural cavities, Ibid., 1935, *31*, 301, fig. 3.

# THE RELATIVE VALUE OF FLUOROSCOPIC, ROENTGENOGRAPHIC AND PHYSICAL EXAMINATIONS IN A TUBERCULOSIS CASE-FINDING PROGRAM IN UNIVERSITY STUDENTS[1,2]

RUTH E. BOYNTON, HAROLD S. DIEHL AND CHARLES E. SHEPARD

During the past few years there has been considerable interest in the possibility of the substitution of fluoroscopic examination of the chest for the chest roentgenograph in tuberculosis case-finding programs. The two obvious advantages of the fluoroscopic examination over the roentgenographic examination of the chest are the time element and the cost. There is some difference of opinion, however, as to the reliability of the fluoroscopic examination as compared with the chest roentgenograph in detecting tuberculous lesions.

Hetherington and Flahiff (1) in comparing the results of the examination of 347 young adults with the fluoroscope and with stereoscopic X-ray films found that the fluoroscope frequently failed to detect pulmonary infiltration when limited to the apex of the lung above the clavicle, but in most instances detected more extensive infiltrations. They also found that the fluoroscope failed to reveal a considerable proportion of the calcified nodules in lungs and lymph nodes visible in roentgenographs.

Reid (2) and Fellows (3) found that the fluoroscopic examination of the chest enabled them to detect tuberculous lesions in a much greater percentage of routine examinations than did the physical examination of the chest alone. Since chest X-ray films were not done unless either the fluoroscopic or physical examination showed evidence of lesions, there is no information as to the number of cases with tuberculous lesions which may have been missed by both the physical examination and examination with the fluoroscope.

An attempt has been made in the present study to add to the knowledge of the relative value of the physical examination of the chest, the fluoroscopic examination of the chest, the Mantoux test and the

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] From the University of Minnesota, Minneapolis, Minnesota.

chest X-ray film in the diagnosis of tuberculous infection or tuberculous disease in routine health examinations.

## METHOD OF STUDY

All students entering the University of Minnesota are given a routine physical examination which includes the usual physical examination of the chest, a fluoroscopic examination of the chest, a Mantoux test and a chest X-ray film if the Mantoux test is positive or if there is any other indication for an X-ray film. The fluoroscopic examinations are done by the regular staff physicians, all of whom have had experience with fluoroscopy but none of whom are specialists in X-ray or fluoroscopic diagnosis. For the Mantoux test .01 mgm. of Old Tuberculin is used. If this is negative a 1 mgm. dose of Old Tuberculin is given. Some students, however, failed to return for a reading of the second test.

The health records of 5,158 students, covering the five-year period from 1931 to 1935 inclusive were selected by random sampling from the total records for these years. Approximately 1,000 records were taken for each year. The ratio of men and women in the group studied was the same as the ratio in the total University population, or about 2 to 1.

From this group of 5,158 records, students who, on routine examination, had one or more of the following findings were selected for detailed study: positive Mantoux test, fluoroscopic findings suggestive of pulmonary lesions, positive X-ray findings, positive or suspicious physical findings. Of the entire group of 5,158, 30 per cent, or 1,585, had one or more of the above findings.

An analysis was then made of these 1,585 records to determine the relative frequency and the correlation of the diagnostic aids listed.

A second part of the study was an analysis of the records of all students on whom a diagnosis of adult-type tuberculosis was made at the Students' Health Service during the same five-year period. The incidence of adult-type tuberculosis in the University population, the time of diagnosis and an evaluation of the various diagnostic aids in making the diagnosis were studied.

Table 1 presents the positive findings suggesting the desirability of further study for evidence of tuberculosis in a general survey of the health records of the 5,158 University students included in the survey.

The records of the 5,158 students were then studied to find what correlation existed between these various diagnostic aids. These data are presented in table 2.

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

TABLE 1

*Positive findings suggesting the desirability of further study for evidence of tuberculosis in a general survey of the health records of 5,158 University students*

| | NUMBER | PERCENTAGE OF 5,158 |
|---|---|---|
| Mantoux test positive | 1,161 | 22.5 |
| Fluoroscopic findings suggestive of pulmonary lesions | 688 | 13.3 |
| X-ray findings suggestive of pulmonary lesions | 272 | 5.3 |
| Physical findings suggestive of tuberculosis | 76 | 1.5 |
| Total number with one or more of above findings positive | 1,585 | 30.7 |

TABLE 2

*Correlation between certain diagnostic findings in the total of 5,158 examinations*

A

| | MANTOUX POSITIVE (1,161) | | MANTOUX NEGATIVE (3,997) | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| Fluoroscopic findings suggestive of pulmonary lesions | 270 | 23.3 | 418 | 10.5 |
| X-ray findings suggestive of pulmonary lesions | 249 | 21.4 | | * |
| Physical findings suggestive of tuberculosis | 44 | 3.8 | 32 | 0.8 |

B

| | FLUOROSCOPIC FINDINGS SUSPICIOUS (688) | | | | FLUOROSCOPIC FINDINGS NEGATIVE (4,470) | | | |
|---|---|---|---|---|---|---|---|---|
| | Mantoux Test | | | | Mantoux Test | | | |
| | Positive (270) | | Negative (418) | | Positive (891) | | Negative (3,579)* | |
| | Number | Per cent | Number | Per cent | Number | Per cent | Number | Per cent |
| X-ray findings suggestive of pulmonary lesions | 96 | 35.5 | 18 | 4.3 | 153 | 17.1 | 5 | 0.1 |
| Physical findings suggestive of tuberculosis | 24 | 8.8 | 31 | 7.4 | 20 | 2.2 | 1 | 0.02 |

C

| | X-RAY POSITIVE (272) | | X-RAY NEGATIVE (939)* | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| Fluoroscopic findings suggestive of pulmonary lesions | 114 | 41.9 | 200 | 21.3 |
| Physical findings suggestive of tuberculosis | 20 | 7.4 | 30 | 3.2 |

* X-ray films not taken in 3,947 cases because of negative Mantoux.

In table 2 B is shown that twice as great a percentage of those with suspicious fluoroscopic findings and positive Mantoux tests had positive X-ray findings as those with negative fluoroscopic findings and positive Mantoux tests.

All cases showing Ghon's tubercles, calcified nodes, increased hilar markings as well as evidence of parenchymal lesions on X-ray examination were classed in the positive X-ray group.

In other words, if the fluoroscopic examination alone had been relied upon 58 per cent of this group showing lesions on X-ray films would have been missed. Of 939 cases with a negative chest X-ray film, 21 per cent were thought to have pulmonary lesions in the fluoroscopic examination. Seven per cent of the positive X-ray group and 3 per cent of the negative X-ray group had physical findings suggestive of pulmonary lesions.

From the group of 5,158 students whose records were studied there were 1,065 in whom a diagnosis of primary type of tuberculous infection was made either because of a positive Mantoux test or positive X-ray findings or both. The correlation between the various diagnostic aids in this group is presented in table 3.

It is important to point out that (table 3 B) in the group in which the fluoroscopic findings were positive, the X-ray did not corroborate these findings in 74 per cent of the cases.

In 166 cases with positive X-ray findings (table 3 C) the fluoroscopic findings agreed in only 42 per cent of the cases while in the negative X-ray group there was agreement in 81 per cent of the cases.

In the general survey group as well as in the group with primary tuberculous infection there was better agreement between the fluoroscopic and roentgenographic examination than between the latter and physical examination. However, the examination with the fluoroscope missed over 50 per cent of the cases showing positive roentgenographic findings. Likewise if a roentgenographic examination had been done on all cases with suspicious fluoroscopic findings instead of on all cases with a positive tuberculin test, an unnecessary expenditure for films would have been made.

The second part of this study was an analysis of the records of all students on whom a diagnosis of adult-type tuberculosis had been made during the five-year period 1931 to 1935. These cases were obtained from our diagnosis cards and obviously were not all included in the general survey group for this same period obtained from a random sampling of the records.

TABLE 3

*Correlation between certain diagnostic findings in cases of primary type infection (1,065 cases)*

A

| | MANTOUX POSITIVE (1,050) | | MANTOUX NEGATIVE (15) | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| Fluoroscopic findings suggestive of pulmonary lesions | 230 | 21.9 | 10 | 66.6 |
| X-ray findings suggestive of pulmonary lesions | 151 | 14.4 | | * |
| Physical findings suggestive of tuberculosis | 33 | 3.1 | 2 | 13.3 |

B

| | FLUOROSCOPIC FINDINGS SUSPICIOUS (240) | | | | FLUOROSCOPIC FINDINGS NEGATIVE (825) | | | |
|---|---|---|---|---|---|---|---|---|
| | Mantoux Test | | | | Mantoux Test | | | |
| | Positive (230) | | Negative (10) | | Positive (820) | | Negative (5) | |
| | Number | Per cent | Number | Per cent | Number | Per cent | Number | Per cent |
| X-ray findings suggestive of tuberculosis | 60 | 26.0 | 10 | 100.0 | 91 | 11.0 | 5 | 100.0 |
| Physical findings suggestive of tuberculosis | 16 | 6.9 | 2 | 20.0 | 17 | 2.0 | 0 | |

C

| | X-RAY POSITIVE (166) | | X-RAY NEGATIVE (899) | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| Fluoroscopic findings suggestive of tuberculosis | 70 | 42.2 | 170 | 18.9 |
| Physical findings suggestive of tuberculosis | 10 | 6.0 | 25 | 2.8 |

* X-ray films not taken in 3,947 cases because of negative Mantoux.

TABLE 4

*Incidence of adult-type tuberculosis in University of Minnesota students, 1931–1935*

| | MEN | NUMBER PER 1000 | WOMEN | NUMBER PER 1000 | TOTAL | NUMBER PER 1000 |
|---|---|---|---|---|---|---|
| Total registration five-year period | 43,037 | | 26,658 | | 69,675 | |
| Total number of cases of adult-type tuberculosis | 56 | 1.3 | 70 | 2.62 | 126 | 1.8 |
| Fibrotic | 11 | 0.25 | 20 | 0.75 | 31 | 0.44 |
| Minimal | 34 | 0.79 | 38 | 1.42 | 72 | 1.0 |
| Moderately advanced | 10 | 0.23 | 11 | 0.41 | 21 | 0.3 |
| Far advanced | 1 | 0.023 | 1 | 0.037 | 2 | 0.028 |

The incidence of adult-type tuberculosis in University of Minnesota students is presented in table 4.

During the five-year period there were 126 cases of adult-type tuberculosis or an incidence of 1.8 per 1,000 students. In all cases the diagnosis was based on positive X-rays and clinical observation. For the past seventeen years, the Students' Health Service at the University of Minnesota has had a tuberculosis clinic under the direction of Dr. J. A. Myers. The classification and the respective rates of these 126 cases are shown in table 4.

TABLE 5

*Number of cases of adult-type tuberculosis first discovered on entrance examination, periodic health examination, in dispensary or infirmary*

| FIRST DISCOVERED IN | FIBROTIC | | MINIMAL | | MODERATELY ADVANCED | | FAR ADVANCED | | ALL TYPES | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Per cent | Total | Per cent | Total | Per cent | Total | Per cent | Total | Per cent |
| Entrance examination | 18 | 58 | 42 | 58.4 | 9 | 42.9 | 2 | 100 | 71 | 56.4 |
| Periodic health examination | 13 | 42 | 19 | 26.4 | 9 | 42.9 | | | 41 | 32.5 |
| Dispensary | | | 7 | 9.7 | 3 | 14.2 | | | 10 | 7.9 |
| Infirmary | | | 4 | 5.5 | | | | | 4 | 3.2 |
| Total | 31 | 100 | 72 | 100 | 21 | 100 | 2 | 100 | 126 | 100 |

TABLE 6

*Relative value of diagnostic procedures in adult-type tuberculosis (X-ray positive in all cases)*

| DIAGNOSTIC PROCEDURES | TYPE OF LESION | | | | | | |
|---|---|---|---|---|---|---|---|
| | Fibrotic (30) | | Minimal (72) | | Moderately advanced (21) | | Far advanced (2) |
| | Number | Per cent | Number | Per cent | Number | Per cent | Number |
| Physical findings | 3 | 10.0 | 7 | 9.7 | 5 | 23.8 | 1 |
| History of exposure | 7 | 23.3 | 16 | 22.2 | 7 | 33.3 | 1 |
| Symptoms, loss of weight, fatigue, cough | 9 | 30.0 | 26 | 36.1 | 8 | 38.1 | 1 |
| Suspicious fluoroscopic findings | 17 | 56.7 | 25 | 34.7 | 12 | 57.1 | 2 |
| Fluoroscopic findings, physical findings | 17 | 56.7 | 28 | 38.9 | 12 | 57.1 | 2 |
| Symptoms, exposure, physical findings | 13 | 43.3 | 39 | 54.2 | 13 | 61.9 | 2 |
| Fluoroscopic findings, symptoms | 20 | 66.7 | 47 | 65.3 | 16 | 76.2 | 2 |
| Fluoroscopic findings, symptoms, physical findings | 20 | 66.7 | 48 | 66.7 | 16 | 76.2 | 2 |
| Fluoroscopic findings, symptoms, exposure | 21 | 70.0 | 55 | 76.4 | 16 | 76.2 | 2 |
| Fluoroscopic findings, symptoms, physical findings, exposure | 21 | 70.0 | 55 | 76.4 | 16 | 76.2 | 2 |

In each type of tuberculosis the rate for women was greater than that for men. It is interesting to note that only two cases of far advanced disease have been seen in a five-year period in an institution conducting a special tuberculosis control program.

It seemed of interest to determine whether the diagnosis of adult-type tuberculosis was made in these students at the time of admission or at some subsequent examination. This is presented in table 5.

It is of interest that the majority of the cases found at later routine examinations occurred in students of medicine or nursing.

The relative value of physical examination, history of exposure to tuberculosis, symptoms and fluoroscopic findings in these 126 cases of adult-type tuberculosis is presented in table 6.

It is seen from table 6 that 25 to 30 per cent of cases of adult-type tuberculosis would have been missed without the routine use of the Mantoux test and chest X-ray films.

## SUMMARY

1. A random sampling of over 5,000 health examination records of University students revealed 30 per cent of the group to have one or more positive findings suggesting the desirability of further study for the evidence of tuberculosis.

2. Routine chest X-ray films of positive reactors were more effective than X-ray examination of cases having suspicious fluoroscopic findings in tuberculosis case-finding.

3. In the general survey group as well as in the group with primary tuberculous infection the fluoroscopic examination missed over 50 per cent of the cases showing positive roentgenographic findings. There was better agreement, however, between the fluoroscopic and roentgenographic examination than between the physical and roentgenographic examination.

4. Only 14 per cent of students with positive Mantoux tests showed X-ray evidence of tuberculous infection.

5. The incidence of adult-type tuberculosis in University of Minnesota students during the years 1931 to 1935 was 1.8 per 1000 students. Eighty-nine per cent of these cases of adult-type tuberculosis were found at routine health examinations.

6. Fluoroscopic examination was a valuable aid in the diagnosis of adult-type tuberculosis. When combined with a history of exposure and symptoms, the fluoroscopic examination detected three-fourths of the

minimal and moderately advanced cases and all of the far advanced cases.

7. Abnormal physical findings were absent in a high proportion of the cases of adult-type tuberculosis and apparently must be considered a diagnostic aid of little importance.

## REFERENCES

(1) HETHERINGTON, H. W., AND FLAHIFF, E. W.: Amer. Rev. Tuberc., 1933, *27*, 71.
(2) REID, A. C.: Ibid., 1929, *20*, 46.
(3) FELLOWS, H. H.: Amer. Jour. Pub. Health, 1935, *25*, 109.

# THE DEGREE OF TUBERCULOSIS IN NEW CASES

P. K. TELFORD[1]

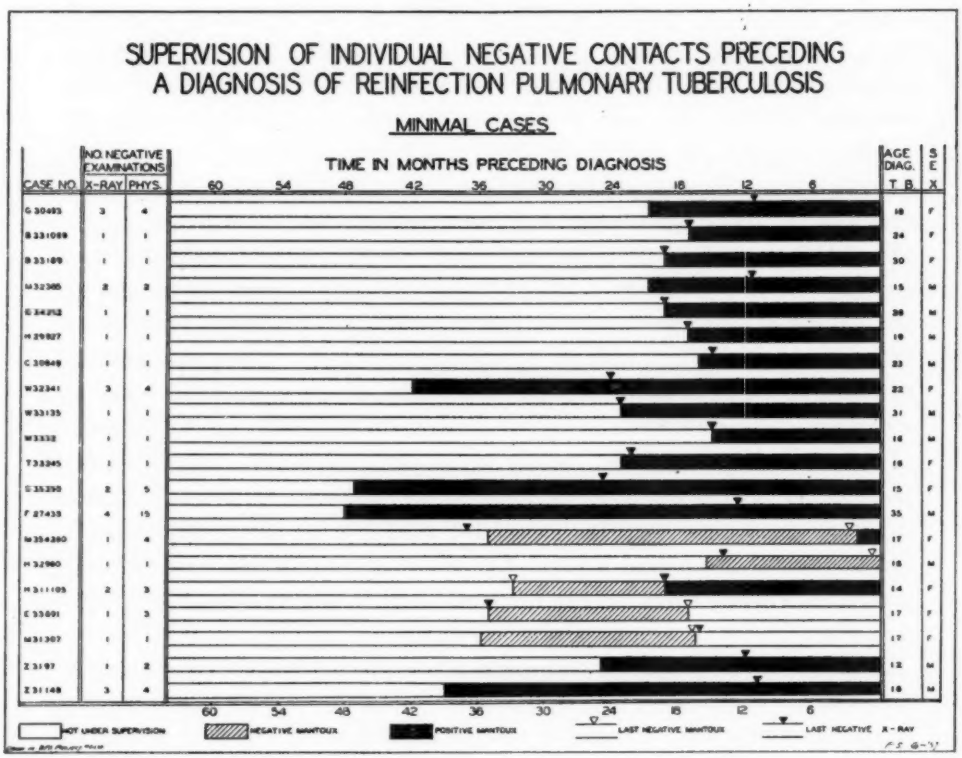
The development of pulmonary tuberculosis in negative contacts under observation in public health clinics makes one skeptical of ever markedly increasing the percentage of progressive cases diagnosed in the minimal stage. Fischel (1) said, "Our efforts to detect the beginning of pulmonary tuberculosis remind us of the many unjustified convictions and acquittals based on circumstantial evidence." It is unquestionably most desirable to discover cases as soon as possible so that more favorable results of treatment may be attained and contacts be sooner protected. So called early diagnostic procedures such as school examinations, particularly in the older age groups, and industrial examinations are extremely valuable in revealing unknown cases, but whether these discovered cases are early or not is purely accidental and certainly cannot be judged by the extent of the lesion. In estimating the age of a newly discovered lesion some commonplace facts must be considered. A large proportion of minimal cases remain minimal and many of them do so in spite of violation of the standard rules of treatment. Pinner (2) states, "In order of frequency, spontaneous healing takes place (*1*) in the primary complex, (*2*) in mild early dissemination, (*3*) in the early infiltrate." These minimal cases may remain active for many years fluctuating within the bounds of a minimal lesion. On the other hand, many moderately and far advanced cases have a minimal stage in theory only that escape detection in routine supervision as demonstrated by our experience. The rapid development of the disease has often been noted. Douglas (3) states, "Progressive and destructive pulmonary tuberculosis usually begins suddenly, with exudative subapical lesions. Lesions far advanced as to extent and excavations, frequently develop within less than six months."

The record of some contact cases is here presented with diffidence because of the irregular examinations in their contact supervision. However, the examinations are steps in a form of supervision which has been developed to a gratifying degree of perfection with support of a generous, sympathetic official attitude for many years. Isolation of the

[1] Los Angeles County Health Department, Los Angeles, California.

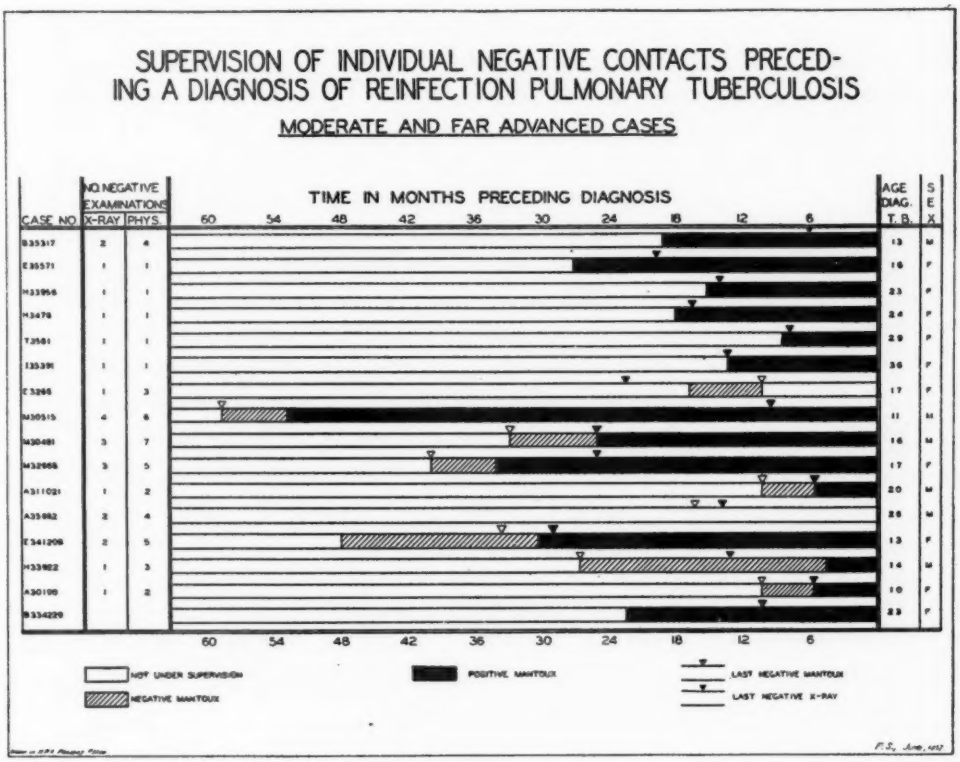
tuberculous and supervision of their contacts have long been the major activity of this department. Although this record is far short of ideal, it is an example of the most that can be expected in considering the preventive program generally, for private agencies are much more handicapped without legal authority to require examinations which we almost daily exercise.

To study this problem, all positive cases under supervision in the pulmonary clinics in the county registry were sorted to choose those




showing a previous negative diagnosis and who were in household contact with an active case. The original active case was in the home at the beginning of the supervision but may have died or been hospitalized at any time thereafter. No point is made of the length of contact because of lack of reliable information on freedom of contact in congested neighborhoods of various races, particularly among Mexicans as many of these patients are. After examination of the records there were eliminated all childhood types, all those with inconclusive findings, either

positive or negative, and all those with such long absences that supervision could not be considered continuous. The records of all of the remainder are charted to show the time in months, previous to discovery of the disease, that the Mantoux test was known to be positive, the last negative X-ray and the last negative Mantoux, if any. The age at the time of the diagnosis is given and the number of negative X-rays and the number of negative physical examinations. The negative Mantoux information is of but slight value because these tests were done with




0.1 mgm. Old Tuberculin before our present practice was started, which requires a negative reaction to a dosage of 10.0 mgm. Old Tuberculin before being considered negative.

In charting this study, an effort has been made to show the sequence of events in the supervision of each case leading up to the diagnosis of tuberculosis. The diagnosis is reached on the chart at the line to the right of the chart at zero months.

There are 36 individuals in this record, 20 minimal and 16 moderately

or far advanced. The minimal cases were evenly divided between males and females while there were 6 males and 10 females moderate and far advanced. The average age at the time of diagnosis of minimal cases was 25 years, moderate and far advanced, 19 years. The average length of previous supervision was for minimal cases 25 months and for moderate and far advanced cases 23 months. The average amount of time elapsing between the last negative X-ray and positive diagnosis was for minimal cases 18 months, for moderate and far advanced cases 14 months, and for all the cases 16 months.

The final stages of prevention of tuberculosis will not be crowned with success so much by early diagnostic measures as by examining more people to locate cases, groups of people where possible, and by greater restrictions placed on known cases disseminating the disease. We have proved to our own satisfaction in a small number of homes of the worst type, as an experimental demonstration over a number of years, that providing a separate room for the patient with proper equipment and a modified quarantine and close supervision stops the spread in the home and the neighborhood. The number of positive-sputum cases living in homes is now not too great to make such an effort practicable. Collapse therapy has made great strides in converting positive-sputum cases to negative ones. Public education in tuberculosis seems to have reached the stage where such control measures will be generally supported.

Many incontrovertible facts of susceptibility related to this problem have been purposely ignored in this brief statement. They are the determining factor in the spread of tuberculosis in such a small percentage of instances that they may be slighted for the moment in order to emphasize the need of stopping the spread from the known sources and the complementary need of discovering unknown sources. An effective isolation can be accomplished but it is unlikely that all cases can be discovered in a minimal stage and be aborted.

## SUMMARY

The record of a number of cases that developed tuberculosis while under supervision as negative contacts is given, which shows that in a serious effort at supervision the frequency of examination is less than desired, and there is a relatively large proportion of moderately and far advanced cases.

Assembling of basic statistics was assisted in by W.P.A. Project No. 5524.

## REFERENCES

(1) Fischel, K.: Amer. Rev. Tuberc., 1931, *23*, 139.
(2) Pinner, M.: Jour. Amer. Med. Assn., 1936, *107*, 477.
(3) Douglas, B. H., Pinner, M., and Wolfpor, B.: Amer. Rev. Tuberc., 1929, *19*, 172.

# THE PSYCHOTHERAPY OF REHABILITATION OF PATIENTS IN TUBERCULOSIS HOSPITALS [1]

CLARENCE M. HINCKS

There is no field of medical endeavor wherein attention to both mental and physical factors is more clearly indicated than in the treatment and rehabilitation of individuals afflicted with tuberculosis. Such psychological considerations as the attitude of the tuberculous patient toward his illness, the status of his mental health, the intensity of his desire to live, the nature of his outlook toward the resumption of activites in the community and his preparation for gainful employment, all have a bearing on prognosis and should be explored and taken into account in therapeutic programs as a necessary adjunct to procedures on the physical side.

It is a striking fact that the proportion of patients in tuberculosis hospitals requiring special attention because of personality difficulties, emotional upsets and lack of vocational training is very considerable. And we can gain some appreciation of why this should be the case when we realize that many individuals were maladjusted prior to the onset of their physical illness, that from the beginning to the end of their treatment patients are exposed to many situations and hazards that may threaten emotional equilibrium, and that many are ill equipped through lack of appropriate training to fend for themselves when they leave the hospital. A brief reference to these points may be relevant.

Facts at our disposal furnish justification for the surmise that at least 20 per cent of the people of this country are maladjusted to varying degrees and that the proportion is greater in reference to those who seek and receive treatment in tuberculosis hospitals.

As I have intimated, it is reasonable to expect an increased tendency to maladjustments among tuberculosis patients as compared with the rank and file of the population because of the numerous threats to peace of mind to which they are peculiarly exposed. What are some of the situations that may tend to upset the emotional balance of this group?

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

The first threat to adjustment and a feeling of security is the individual's realization that he is a victim of tuberculosis. According to Williams and Hill who studied the histories of 1,499 patients, we are informed that 4 per cent collapsed and gave up hope when they became aware of the diagnosis and that 18 per cent were disturbed to varying degrees. I suspect that these figures do not tell the whole story and that a much larger percentage was subject to spells of morbid reverie wherein fears, anxieties, apprehensions and lowness of spirits colored thoughts relating to the future, to frustrated ambitions, to separation from the family circle and friends, to the plight of dependents and so on.

Following the acceptance of a diagnosis, the next series of adjustments that patients are called upon to face are those connected with hospitalization and treatment. It may be difficult for many to fall in line with requirements for prolonged periods of rest, or to submit to operative procedures, or to accept relapses when they occur, or to maintain morale and courage over a long haul. Indeed, the circumstances connected with hospitalization and treatment may constitute an acid test, as it were, to the adjustive capacity of individuals and may serve to abet the development of psychoneuroses and neurotic episodes among those who are vulnerable in this regard. And so we should not be surprised to learn that, in a study of 100 patients at the Cragmor Sanatorium, Forster and Shepard discovered that 31 were the victims of such emotional states as fear, anxiety, fatigue and frustration. Of this total of 31, 20 were diagnosed as psychoneurotic, 4 were psychotic and 7 had simple maladjustments.

Facts of this nature indicate that there is an urgent challenge for constructive efforts along lines of mental health and education in sanatorium practice.

The task of attending to the mental needs of patients should, when possible, be shared by the physician, nurse, vocational counsellor, teacher and social worker. It devolves upon the physician, of course, to give leadership. Without his whole-hearted interest and direction little can be expected from any psychotherapeutic program. He can make specific contributions by including a psychiatric approach in his examination procedures, by giving opportunities for the relief of tensions and anxieties through therapeutic conversations, and by taking a genuine interest in vital matters relating to his patient such as work, recreation, friendship, ego satisfactions and philosophy of life.

If the physician includes a psychiatric or human approach in his

examination procedures there will result not only the collection of pertinent data for a mental diagnosis, but also the basis for a satisfactory therapeutic relationship or rapport with each patient. As a routine measure the exploration of the mental life might embrace a brief canvass of the developmental history with attention to adjustments that had been made in school, home and play life, and following this an enquiry concerning occupational history, church and club affiliations, interests and ambitions. Half an hour spent in conversing upon issues of this nature might well reveal some of the fundamental attitudes of the patient to his fellows and to his life in general, together with clues concerning personality make-up and some of the specific psychological needs that should be satisfied during the period of hospital treatment.

In general the physician will discover that the mental health of patients can be fortified by making suitable provisions for work, recreation and other intrinsic needs that have already been enumerated and that I should like to discuss briefly.

We have reason to look upon work as a great morale builder, as an antidote to morbid introspection and worry and as a necessity for the prevention of mental rusting and deterioration. Insofar as it makes a pull upon imagination and initiative and is directed to some desired goal, it furnishes personal satisfactions of enormous benefit to mental health.

In sanatorium practice, whenever possible, work or occupational therapy should be integrated into educational and vocational training programs with the supervision of the physician to determine the types of activities most suited to the patient's physical and mental condition.

Another requirement for mental well-being is recreation. It provides the occasion for the release of the human spirit in care-free activities of tonic value. The physician should therefore encourage hospital arrangements that foster avocations and the development of varied interests.

It is a well recognized fact that, to maintain perspective and emotional balance, most individuals need intimate friends, who are genuinely interested in them and who, by sharing experiences, can take the edge off fears and anxieties. The hospital staff can to a degree satisfy this hunger for close human relationships.

Because of their influence on mental welfare there should be taken into account the satisfaction of ego hungers and a robust philosophy of life. By ego hunger we refer to the craving of every individual to be a person, to be more than a cog in a machine, to receive recognition and to have a sense of worth-whileness. In sanatorium life satisfaction may come

through the personal attention of hospital workers, through the knowledge that courage is being displayed by the patient in facing the issues of illness, through a sense of achievement in educational programs and in many other ways.

A robust philosophy of life implies an emotional anchorage and undismayed outlook even during periods of crisis. For many individuals religion is of importance in this connection and for others strength is derived through the application of the dictum that has come to us from ancient Greek philosophy: "Know thyself, accept thyself and be thyself." There is no question that the contacts of patients with those who possess a robust philosophy are wholesome.

As has been indicated, the task of attending to the mental needs of patients provides a challenge not only to the physician but to his coworkers as well. The nurse has an unrivaled opportunity to inspire confidence and to combat morbid introspection. The vocational counsellor, through interviewing and the application of aptitude tests, can supplement the diagnostic work of the physician and can indicate the type of training most suited to individual needs and capacities. The educational program conducted by the teacher may not only prepare the individual to take his place as a productive member of society, but in addition provides opportunities for the development of interests and attitudes that will fortify mental health. And the social worker is indispensable in attempting to secure vocational placement and to effect satisfactory home adjustment that is so important in preventing relapse.

During recent years encouraging progress has been made in developing mental health programs in tuberculosis hospitals. Medical staffs have demonstrated an increased interest in this phase of the work. Educational activities have been extended. Industrial work shops have been organized. Through the Division of Rehabilitation of the National Tuberculosis Association, an impetus has been given to the development of vocational guidance and training services. A beginning has been made in the exchange of physicians attached to mental hospitals and sanatoria for consulting work with advantage to both types of institutions.

In looking to the future it is possible that sanatoria in combining the functions of college and hospital will become recognized as significant training centres for life itself. And perhaps the circumstance of becoming afflicted with tuberculosis may prove to many to be a blessing in disguise because treatment will involve a period of priceless life enrichment. Such advance would have a profound effect on the whole field of medicine.

# PROGNOSIS OF THE CAVITY BEARER[1, 2]

HERMAN SCHWATT[3] AND ARTHUR REST

The ultimate fate of the tuberculous cavity bearer has always been of great interest to the phthisiologist. The immediate stimulus to the statistical investigation of this subject has been the oft quoted dictum of Graeff (1), in 1921, that pulmonary tuberculosis is a curable disease and does not necessarily shorten life; that, however, the disease becomes incurable and, in the majority of cases, signifies a death sentence within a few years, as soon as it becomes complicated with a cavity of a size greater than that of a cherry. Graeff's pronouncement was based essentially on his pathologicoanatomical findings that in deaths from causes other than tuberculosis cavities were rarely found at autopsy. His conclusion was that cavity carriers were not subjects for sanatorium treatment and that only surgical measures can in severe cases lead to cure of the disease.

Graeff (2) in a later paper, receded somewhat from his original position, as a result of the clinical and roentgenological evidence of healing of cavities. Nevertheless, he still emphasized that the complete obliteration of large cavities is extremely rare. He called upon clinicians to prove otherwise, by clinical statistical studies, on the longevity of cavity carriers, including their physical condition and economic usefulness after various periods of life.

Although it is shown by X-ray findings that cavities of considerably greater size than a cherry may heal clinically as well as anatomically, there has been no lack of authoritive support of Graeff's famous dictum. Barnes and Barnes (3), in a study of 616 patients with cavities larger than two centimetres, found that only 79 per cent survived a year. The average duration of life was 15.8 months. Of 89 cases with tuberculous laryngitis, 79 died within a year; of 17 cases with tuberculous enteritis none survived a year. In Fischel's (4) series of honeycombed

[1] From the Medical Service of the Sanatorium of the Jewish Consumptives' Relief Society, Spivak, Colorado.

[2] Presented at meeting of the Denver Sanatorium Association, Spivak, Colorado, October 27, 1936.

[3] Deceased.

lesions, cavitation of an entire lobe or of an entire side, only 20 per cent survived a year. The average duration of life was 9.5 months. Simpson (5) states that two-thirds of all patients with cavity will ultimately die of tuberculosis within 15 years and that the great majority will not live longer than 5 years.

TABLE 1

*Survival and deaths in 267 patients with cavernous pulmonary tuberculosis during an observation period of from 3 to 10 years following discharge*

| DISCHARGED | | | | MALE | FEMALE |
|---|---|---|---|---|---|
| In | Number of cases | | | | |
| 1925 | 29 | Living | 9 | 7 | 2 |
| | | Dead | 20 | 19 | 1 |
| 1926 | 35 | Living | 12 | 10 | 2 |
| | | Dead | 23 | 20 | 3 |
| 1927 | 28 | Living | 10 | 9 | 1 |
| | | Dead | 18 | 13 | 5 |
| 1928 | 40 | Living | 14 | 10 | 4 |
| | | Dead | 26 | 19 | 7 |
| 1929 | 40 | Living | 11 | 5 | 6 |
| | | Dead | 29 | 22 | 7 |
| 1930 | 30 | Living | 13 | 11 | 2 |
| | | Dead | 17 | 9 | 8 |
| 1931 | 29 | Living | 14 | 11 | 3 |
| | | Dead | 15 | 10 | 5 |
| 1932 | 36 | Living | 21 | 14 | 7 |
| | | Dead | 15 | 9 | 6 |
| Total..... | 267 | Living | 104 (38%) | 77 | 27 |
| | | Dead | 163 (62%) | 121 | 42 |

From the year 1925 to the year 1933, 1,524 patients were discharged from this institution. Our systematic follow-up studies familiarized us with their clinical state and subsequent course. In this presentation, we shall confine ourselves to an investigation of those untreated cases which upon discharge presented definite cavitation, in order to determine the duration of life of untreated patients with cavernous phthisis. The

number of patients suitable for this study is 267, all of them having far advanced pulmonary tuberculosis with cavitation in one or both lungs. There were cavities involving the greater portion of the apical region, or of the upper lobe, and most of them presented almost complete excavation of the summit of the lung or of the entire lungs. Practically all of the cavities were of the chronic tertiary type with thick walls sur-

TABLE 2

*Survival and deaths in 267 patients with cavernous pulmonary tuberculosis during an observation period of from 3 to 10 years following discharge, according to extent of lesion*

| DISCHARGED IN | | R-1 L-3 | R-2 L-3 | R-3 L-3 | L-1 R-3 | L-2 R-3 |
|---|---|---|---|---|---|---|
| 1925 | Living | | | 3 | 3 | 3 |
| | Dead | 1 | 1 | 17 | | 1 |
| 1926 | Living | 3 | 2 | 3 | 3 | 1 |
| | Dead | 1 | 1 | 21 | | |
| 1927 | Living | 2 | 2 | 3 | 3 | |
| | Dead | | 1 | 13 | 2 | 2 |
| 1928 | Living | | | 7 | 6 | 1 |
| | Dead | 1 | 1 | 23 | 1 | |
| 1929 | Living | | 1 | 8 | | 2 |
| | Dead | 2 | 1 | 24 | 1 | 1 |
| 1930 | Living | 1 | | 7 | 2 | 3 |
| | Dead | 2 | 3 | 12 | | |
| 1931 | Living | | 1 | 8 | 3 | 2 |
| | Dead | 2 | 2 | 11 | | 2 |
| 1932 | Living | 1 | 1 | 15 | | |
| | Dead | | 3 | 12 | | |
| Total.... | Living | 7 | 7 | 54 | 24 | 10 |
| | Dead | 9 | 13 | 133 | 4 | 6 |

rounded by considerable fibrosis. In other words, they were all of a size which according to Graeff (1) signifies a death warrant within a few years.

The following tables will illustrate certain phases of this study. The outstanding facts can be briefly summarized as follows:

(*1*) An analysis of 267 discharged patients with tuberculous cavities revealed that 104, or 38 per cent, were still alive after a 3 to 10 year period (table 1).

Of these, 60, or 58 per cent, were working and 44, or 42 per cent, were curing. The average duration of life of those who died was seven and a half years, from the time of the recognition of the cavity.

(*2*) Of those with a mainly unilateral lesion, 70 per cent were alive over a 3 to 10 year period, while only 30 per cent survived of those with extensive bilateral disease (table 2).

TABLE 3

*Relation of bacilliferous sputum to survival of cavity bearers*

| DISCHARGED | | | | SPUTUM | |
|---|---|---|---|---|---|
| In | Number of cases | | | Positive | Negative |
| 1925 | 29 | Living | 9 | 3 | 6 |
| | | Dead | 20 | 20 | |
| 1926 | 35 | Living | 12 | 6 | 6 |
| | | Dead | 23 | 20 | 3 |
| 1927 | 28 | Living | 10 | 8 | 2 |
| | | Dead | 18 | 17 | 1 |
| 1928 | 40 | Living | 14 | 9 | 5 |
| | | Dead | 26 | 26 | |
| 1929 | 40 | Living | 11 | 8 | 3 |
| | | Dead | 29 | 27 | 2 |
| 1930 | 30 | Living | 13 | 10 | 3 |
| | | Dead | 17 | 17 | |
| 1931 | 29 | Living | 14 | 9 | 5 |
| | | Dead | 15 | 12 | 3 |
| 1932 | 36 | Living | 21 | 14 | 7 |
| | | Dead | 15 | 9 | 6 |
| Total..... | 267 | Living | 104 | 65 (30%) | 39 (72%) |
| | | Dead | 163 | 148 (70%) | 15 (28%) |

(*3*) The survival, according to the extent of the lesions, was, as follows:

L 1–L 3—80 per cent
L 2–R 3—60 per cent
R 1–L 3—40 per cent
R 2–L 3—35 per cent

(*4*) Thirty per cent of those who left the institution with positive sputum were still alive over the period of study. Seventy-two per cent of those who

left the sanatorium with negative sputum were still alive at the end of the observation period (table 3).

(5) Seventeen per cent of those discharged with a tuberculous laryngitis were still alive; only 1 per cent of those with tuberculous enteritis were still alive; 4 per cent of those with genitourinary complications were alive (table 4).

TABLE 4

*Survival of cavity bearers as dependent on tuberculous complications*

| DISCHARGED | | | | COMPLICATIONS | | | |
|---|---|---|---|---|---|---|---|
| In | Number of cases | | | Laryngeal | Intestinal | Genito-urinary | No complications |
| 1925 | 29 | Living | 9 | 1 | | | 8 |
| | | Dead | 20 | 8 | | | 12 |
| 1926 | 35 | Living | 12 | 2 | | 1 | 9 |
| | | Dead | 23 | 3 | 2 | 1 | 17 |
| 1927 | 28 | Living | 10 | 3 | | | 7 |
| | | Dead | 18 | 6 | 1 | 1 | 10 |
| 1928 | 40 | Living | 14 | 1 | | | 13 |
| | | Dead | 26 | 8 | | 2 | 16 |
| 1929 | 40 | Living | 11 | 2 | | | 9 |
| | | Dead | 29 | 5 | | | 24 |
| 1930 | 30 | Living | 13 | 3 | | 2 | 8 |
| | | Dead | 17 | | 2 | | 15 |
| 1931 | 29 | Living | 14 | 5 | | 1 | 8 |
| | | Dead | 15 | 2 | 2 | | 11 |
| 1932 | 36 | Living | 21 | 2 | 1 | | 18 |
| | | Dead | 15 | 6 | 1 | | 8 |
| Total.... | 267 | Living | 104 | 19 | 1 | 4 | 80 |
| | | Dead | 163 | 38 | 8 | 4 | 113 |

(6) Those patients who left the institution between the ages of 20 to 35 had an average mortality of 32 per cent; those between the ages of 35 to 65 showed an average mortality of 8 per cent.

(7) The patients who had their disease from 1 to 5 years presented a mortality of 40 per cent; those who had the disease from 10 to 15 years showed a mortality of 17 per cent.

## CONCLUSIONS

1. Although cavity is the most serious complication of pulmonary tuberculosis, it is not of such grave import as Graeff pronounced it to be.

2. The larger the ulcerating cavity surface, the more ominous the prognosis; with bilateral lesions the mortality is greatest.

3. Right-sided lesions are apparently less serious than left-sided lesions.

4. The presence of tuberculous laryngitis and enteritis makes the prognosis graver than in those patients without these complications. Of the two complications, laryngitis presents a more favorable outlook.

5. Patients with positive sputa present a much higher mortality than those who on discharge had negative sputa.

6. Age, in this group of cases, as well as in tuberculosis in general, has a definite relation to the duration of life. The highest mortality was in the 20 to 35 age group with a gradual decline after the age of 40.

7. It appears that the patients who survive the first five years of their disease have an increasingly favorable prognosis with the increase of the duration of their disease.

8. Although this study tends to show that a fair proportion of patients with extensive excavations may survive for long periods of time under normal conditions of useful life, it is our opinion, in view of the extremely unfavorable prognosis in the great majority of cases, that every patient with demonstrable cavity and positive sputum should be subjected to undelayed collapse therapy when the disease is unilateral and to some combination of collapse therapy in bilateral cases.

## REFERENCES

(1) GRAEFF: Ztschr. f. Tuberk., 1921, *34*, 683.
(2) GRAEFF: Ibid., 1927, *47*, 177.
(3) BARNES AND BARNES: Amer. Rev. Tuberc., 1928, *18*, 412.
(4) FISCHEL: Ibid., 1931, *24*, 461.
(5) SIMPSON: Ibid., 1935, *31*, 658.

# TUBERCULOUS MEDIASTINITIS[1]

## Report of a Case with Focal Reaction to Tuberculin

R. H. KAMPMEIER

In chronic pulmonary tuberculosis it is not unusual to find some changes in the mediastinum at necropsy. Widespread tuberculous involvement of the mediastinum, however, in the absence of pulmonary disease is uncommon.

Tuberculosis of mediastinal lymph nodes is described in some textbooks as tuberculous mediastinitis. But it does not seem that this condition, even with some periglandular reaction, justifies the term mediastinitis. Occasionally cases of so called tuberculous "mediastino-pericarditis" are found.

The term "tuberculous mediastinitis" should be reserved for widespread involvement of the loose mediastinal tissues due to tuberculosis, leading to symptoms resulting from compression. Opie, in his discussion of a paper by Kornblum and Cooper (1) in 1930 said, "For the first time it establishes tuberculous mediastinitis as a clinically recognizable condition. Tuberculosis of the mediastinal lymph nodes is not tuberculous mediastinitis. The designation is appropriate only when the lesion extends into the adjacent cellular tissue."

Though necropsy was not possible in the case to be reported, the aetiology seems to be without question. The publication of this case seems indicated not only because of its unusual characteristics, but also to serve as a warning to the possible use of tuberculin in a case of suspected tuberculous mediastinitis. Marked focal reaction to tuberculin in this case clearly indicates the aetiology.

### LITERATURE

The various causes of mediastinitis are usually stated as pyogenic or rheumatic in acute, and syphilitic or tuberculous in chronic cases. A careful search of the literature offers little specific information on the subject of tuberculous mediastinitis though it is frequently mentioned in textbooks.

[1] From the Department of Medicine of Louisiana State University Medical Center, and the State Charity Hospital, New Orleans, Louisiana.

Osler (2) in 1903 reported a case similar in some respects to the one to be reported here. His case was that of a colored male, 22 years old, seen because of swelling of the neck, dyspnoea and tightness in the chest which had suddenly appeared 6 days previously. There were found puffiness of the face, tenderness in the suprasternal notch and dilated veins over the upper chest. He was afebrile and the X-ray examination of the lungs was negative. A pleuropericardial friction rub was heard once. A year later the same symptoms were present, the veins were more prominent and the X-ray examination was still negative. In another 6 months the patient had cough, pain in the right arm, and showed a fuller right radial pulse than left. There was impairment over the right lung and tubercle bacilli were present in the sputum. On the fourth admission, 26 months after onset of symptoms, he had haemoptysis, cough and chest pain. The physical signs noted before were more evident. He developed tuberculous meningitis. Autopsy showed tuberculosis of lung, spine and meninges. There was fibrosis adjacent to and causing occlusion of the superior vena cava and innominate veins. The peritoneum and pericardium were normal.

In 1915 Howard (3), in a discussion of the diagnosis of mediastinitis, reported two cases probably of tuberculous origin. One case was that of a white male, 28 years of age, who for 7 years had had cyanosis and oedema of the face and neck. There had been variable dyspnoea and orthopnoea in these years. Examination showed marked cyanosis of face, eyes, lips, ears and finger tips. Collateral venous circulation was present over the upper chest. The heart and lungs were negative. X-ray study showed a dense shadow in the mediastinum but not suggestive of aneurism. The second case was associated with long-standing empyema and cutaneo-pleurobronchial fistula. X-ray examination of the mediastinum was negative. Both cases presented a crunching sound over the mediastinum upon lifting and lowering the arms. There was no evidence of syphilis in either case.

Kornblum and Cooper (1) reported five cases in 1930.

Case 1. A 23 year old white female was seen, a year after the drainage of a "cold abscess" of the upper sternal region, because of hoarseness, to be followed still later by X-ray evidence of widening of the mediastinal shadow and by paralysis of the left recurrent laryngeal nerve. Subsequently there were aphonia, weakness, dyspnoea, chest pain and paroxysmal cough. Though two and one-half years had passed since the first X-ray examination, there was still no clinical nor X-ray evidence of pulmonary tuberculosis. Two months later she developed tuberculous pneumonia and died.

Case 2. White male, 57 years of age, complained of paroxysmal, brassy cough of 8 months' duration. Sputum was negative for tubercle bacilli. An X-ray film showed an old pulmonary lesion and widened mediastinal shadow.

Before death the sputum was positive. Necropsy revealed tuberculous mediastinitis.

Case 3. A white female, 31 years old, had cough with positive sputum. She did well and 9 years later developed a sense of oppression in the chest, with dyspnoea and cough. X-ray study showed a wide superior mediastinal shadow. The sputum was positive for tubercle bacilli.

Case 4. A 49 year old white male had cough, and an X-ray examination showed widening of the mediastinal shadow. Later an apparent mass extended outward toward the left apex. The sputum was positive for acid-fast bacilli. Later there was definite tuberculous involvement of the lung.

Case 5. A white male had dyspnoea and cough. X-ray study demonstrated involvement of both lung roots and widening of the mediastinal shadow. Later there was spread to the lungs. Necropsy showed chronic inflammation of the mediastinal tissues with tuberculous abscesses.

In 1932 Milles (4) reported the case of a white male seen because of vertigo, dyspnoea, orthopnoea and oedema of face and neck, of about a year's duration. There was cyanosis of the face. The X-ray plate showed a widened mediastinal shadow. At necropsy a mass, with caseous areas, was found to encircle and obstruct the superior vena cava.

## CASE REPORT

The case reported here was under constant observation on the author's service for four months.

*C. C.* was an intelligent mulatto male, 18 years of age, and a laborer by occupation. He was admitted to Charity Hospital on March 8, 1935. His chief complaint was shortness of breath, cough, and pain and swelling of the left arm. In January, 1935, the patient began to be aware of weakness, and he was told that he was pale. He felt tired much of the time. At about the same time a dull aching pain developed in the left chest, radiating to the lower costal margin of that side. About a week after the onset of pain the patient began to be troubled with "sore-throat" and cough. The cough was dry and hacking in character, but after a few days he began to raise white frothy sputum. This soon became yellow and thick, and occasionally was streaked with blood. The productive cough persisted until admission. It had been worse at night. Coughing was associated with soreness referred to the sternal region and the left chest. The patient believed he had been somewhat hoarse recently. From the onset of illness night-sweats were profuse, requiring a change of clothing at least twice a night. Chilliness was often noted in the daytime. Three weeks before admission dyspnoea was noted upon exertion as slight as walking across the room. This had been persistent. He consulted a physician because of this symptom on February 21. A diagnosis of pleurisy

was made and a "pint of yellow fluid" was removed from the left chest. Three days after the aspiration the patient developed pain in the left shoulder and at the root of the neck. One and a half weeks before admission he awoke one morning to find his left arm swollen from shoulder to hand. The shoulder was extremely painful upon movement and there was marked tenderness in the axilla. The swelling gradually extended to involve the pectoral and supraclavicular regions on the left side. Two weeks before entering the hospital, he began to have diarrhoea, with movements every 15 to 30 minutes throughout the day and night. The stool was of small quantity, consisting of green mucoid material. Tenesmus was present. Diarrhoea lasted one week, finally being relieved by paregoric. There had been no nausea or vomiting, but there was increasing anorexia. Some loss of weight occurred.

The patient had always been in good health prior to the onset of his present illness. There had been no exposure to tuberculosis. Venereal disease was denied.

His father had died of unknown cause. The mother, 4 brothers and 3 sisters were living and well.

*Physical examination:* The patient was a very light mulatto, obviously quite ill, and very anxious concerning himself. He was of sthenic habitus.

The conjunctivae and mucous membranes appeared to be pale. Pupils were equal and reacted normally. The throat was normal. The thyroid isthmus was palpable. There was visible swelling in the left neck. The supra- and infraclavicular areas were obliterated on the left side. Oedema extended up to and back of the left ear.

Expansion of the chest was limited on respiration, and there was lagging of the left side. The swelling which was present in the neck extended downward over the left chest to the level of the nipple. The interspaces were obliterated on the left side. There was absence of tactile fremitus below the sixth rib posteriorly and fourth rib in the axillary line on the left side. The lungs were resonant on percussion except in the region of decreased tactile fremitus where the percussion note was dull. There was some dulness at the right base posteriorly. Breath-sounds were decreased in the areas of dulness. Respiration was shallow and rapid.

The cardiac impulse was palpable in the fifth interspace 6 cm. from midline. There was a good shift of the impulse with change of position. Cardiac borders were difficult to map out but there was apparently no enlargement. The pulse-rate was 120 per minute at the right wrist. There was no palpable pulse in the left radial or brachial arteries because of the marked oedema. The blood-pressure in the right arm was 95/70, but could not be obtained in the left arm because of the oedema.

The liver was palpable 5 cm. below the right costal margin, firm in consistency and slightly tender. Rectum and genitalia were normal.

The left arm was markedly swollen from the shoulder down to and including the hand, with deep pitting. It was slightly cyanotic. There was pain in the left shoulder on active and passive motion and the left axilla was very tender. The lymph nodes of the left axilla were somewhat enlarged, otherwise there was no lymphadenopathy. Very slight pitting oedema was present at the ankle.

*Laboratory data:* Urine was negative. Two blood Wassermann tests were negative. The sputum was repeatedly negative for acid-fast bacilli. The stool was not remarkable. On admission the red cell count was 4,200,000, haemoglobin 70 per cent (Sahli), white cell count 10,300. The differential showed 70 per cent segmented leucocytes, 10 per cent stab forms, 0.5 per cent juveniles, 0.5 per cent basophiles, 8 per cent small lymphocytes, 2.5 per cent large lymphocytes, and 8.5 per cent monocytes.

The first X-ray examination on March 11 was reported as showing dry mediastinitis and pericarditis.

*Progress notes:* These are given in some detail because of the interest and variation of findings from time to time.

By ten days after admission the oedema of the left arm had begun to subside, and the patient was complaining of pain in the right arm and of tenderness in the right axilla. On the following day, March 19, the right arm had swollen, being more oedematous now than the gradually improving left arm. Four days later the swelling of the right arm had become so marked that the radial pulse could not be felt and it was impossible to obtain a blood-pressure reading. However, the pulse at the wrist and a blood-pressure of 114/94 was obtained for the first time in the left upper extremity. For the first time the patient was aware of some difficulty in swallowing.

On March 26 a note was made that the swelling of both arms had now subsided, but that there was oedema of both legs, the scrotum and penis. A diagnosis of mediastinitis had been made, and, because syphilis had been found to be the cause in such conditions in the past at Charity Hospital, treatment was started with mercury and iodides. Two days later it was observed that there was beginning dilatation of the veins over the upper chest anteriorly, as evidence of collateral venous return. The following day the right arm was as swollen as the lower extremities were, this having occurred over night. He had diarrhoea for two days, relieved by bismuth and paregoric.

On April 1 the oedema of legs, genitalia and right arm was still present and the patient was extremely dyspnoeic and somewhat cyanotic. By the 4th of April there was pitting oedema of the whole body, all extremities and the whole trunk anteriorly and posteriorly, though somewhat less about the face. Some cyanosis was present. No ascites could be demonstrated. On the following day dysphagia was marked.

April 8 saw much improvement, a dose of salyrgan having been given the

preceding day. The general body oedema had subsided to a great degree and there was improvement of the constant troublesome nonproductive cough. Dysphagia persisted. On the following day oedema was practically gone and with its subsidence the collateral venous pattern over the upper chest was much more marked than previously. On the 10th, the oedema was gone from all parts of the body. X-ray study on April 13 showed a right pleural effusion, corroborating physical findings.

Late in the afternoon of April 13 the patient was given 0.1 cc. of a 1:10,000 dilution of Old Tuberculin intracutaneously. Within twenty-four hours he presented a marked local reaction. At the site of injection was a vesicle, which later sloughed, 7 mm. in diameter, surrounded by an area of fiery redness involving the whole forearm from wrist to elbow on the flexor surface. By the 15th, the oedema of both arms, the neck, face and upper chest had reappeared as severe as at any time. Dyspnoea was alarming, he was orthopnoeic, and swallowing was almost impossible. On this day the patient had the first temperature elevation since entering the hospital. It rose during the day to 101°F. Fluid was discovered in the right chest, and 1,000 cc. were removed in the hope of relieving the dyspnoea to some extent. The patient was very hoarse but laryngeal examination showed normal vocal cords.

On the 16th the temperature was again normal and much of the oedema had subsided. The following day 1,200 cc. of straw-colored fluid were removed from the right pleural cavity.

By April 20, the patient was very comfortable, free of oedema, had practically no dysphagia, very little cough, and was afebrile. Ultraviolet radiation produced a skin rash. On the 26th a note was made regarding the progression of the veins over the upper chest, and on the 28th there was oedema of the left foot. The liver was still palpable and tender. X-ray examination still showed the widened mediastinal shadow, and fluid in the right chest.

Throughout the month of May and the first half of June the patient was at his best. He had no oedema of any parts, only slight cough and no dysphagia. Much of the time was spent out of bed, walking about the ward and sitting in a chair. He ate quite well. No fever was present at any time. However, the veins over the upper chest, shoulders and in the neck became more prominent. One thousand to 1,400 cc. of yellow, clear fluid were aspirated from the right chest on May 20 and 27, June 15 and 22. Roentgen-ray examination on June 21 showed thickening of the right pleura, and for the first time obliteration of the left costophrenic angle (figure 1).

At about the middle of June, the patient developed fever for the first time since admission, except for April 15 when the tuberculin test had been done. The fever lasted to the date of desertion from the hospital, fluctuating widely every day, from 98° to 101° or 102°F. At the same time the patient went back to bed because of abdominal pain. There was diffuse, quite severe

abdominal tenderness with little muscle reaction. After about 10 days of this, diarrhoea developed with frequent green watery stools. The patient lost strength and weight very rapidly. Abdominal pain and diarrhoea persisted until he left the hospital. The right chest was tapped on June 27 and July 4. The patient was discharged against advice, upon the insistence of his family on July 6.

A letter from the patient's home physician stated that high fever, tachycardia, abdominal pain and diarrhoea persisted to the time of death on July 21. No necropsy was done.

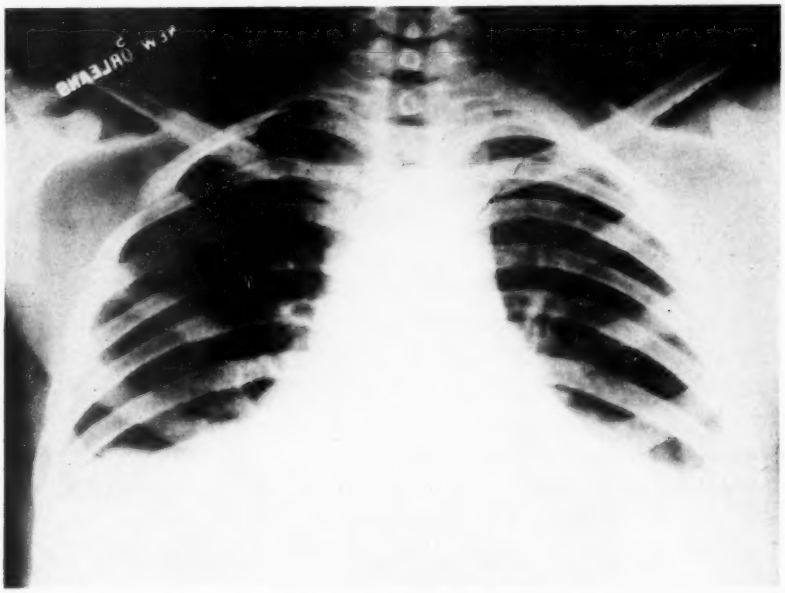


FIG. 1. Showing the wide mediastinal shadow

## DISCUSSION

From the few reported cases of tuberculous mediastinitis, it is apparent that the symptomatology varies according to the mediastinal structure or structures pressed upon by the inflammatory process. The lesion may be diffuse with wide-spread pressure effects, or localized as indicated by a single or few symptoms. It seems that Knox's (5) statement, attributed to Lian, that syphilis attacks the superior, and tuberculosis the inferior mediastinum is not tenable.

The various symptoms in the cases abstracted from the literature have been paroxysmal cough, dyspnoea and orthopnoea due to pressure

on the trachea and bronchi. Obstruction to the superior vena cava or its large branches has led to oedema of face and neck, to cyanosis, as well as to a collateral venous circulation. Hoarseness, aphonia and brassy cough have been associated with involvement of the left recurrent laryngeal nerve. Pain and sense of tightness in the chest are to be expected with an expanding or constricting (depending upon the stage) inflammatory process. The X-ray studies have almost uniformly shown a widened mediastinal shadow. Most of the cases have had their tuberculous origin proved by the development of pulmonary tuberculosis or by necropsy.

The case forming the basis for this report showed several interesting features, and the diagnosis of tuberculous mediastinitis is acceptable in this case in spite of lack of necropsy evidence. The diagnosis is based on the history of mediastinitis in a young patient, without any evidence for syphilis, and on a marked local, focal and constitutional reaction to tuberculin, and finally the clinical picture of tuberculous peritonitis and enteritis.

Conceivably a tuberculous process in peribronchial or hilar nodes was the primary focus. This was followed by a diffuse reaction in the mediastinum. The mediastinal oedema gradually subsided to reappear as an allergic response to an intracutaneous tuberculin test, accompanied by intense local reaction as well as fever in an otherwise afebrile course. This was followed by a subsidence of the reaction. From this point it is probable that a sclerosing process was beginning as shown by a progressing collateral venous circulation pointing to increasing obstruction of the venous return from head, neck and arms. It seems permitted to postulate that this would have continued for months or years, as in the cases reported by Osler, Howard and Milles. Or it may be that he would have developed the more common "mediastino-pericarditis." However, the appearance of clinically typical tuberculous peritonitis in the latter part of the period of observation cut short the eventual picture of a sclerosing mediastinitis.

The changes in the mediastinum were very widespread and fluctuated in degree, as shown by the variable pressure on anatomical structures. At one time or another, the pressure involved the tracheobronchial tree, the oesophagus and the venous return especially of the head, neck, upper extremities and upper chest. More difficult of proof, but very probable, was pressure in the lower mediastinum, because of oedema of lower levels. The oedema was remarkable. In the arms, at one time

or another, it was so extreme that deep pitting was present, as well as signs of severe stretching of the skin. Oedema of the lower extremities occurred at times, and marked swelling of the genitalia appeared once. The liver was constantly enlarged. Also at one time there was pitting oedema of the entire body. Yet all this cleared up to be followed by weeks of activity upon the ward, and with no subsequent recurrence.

The pleural effusions, which were negative for tubercle bacilli on guinea-pig inoculation, were most probably due to increased venous pressure in the azygos veins and their draining intercostal veins. The fluid accumulated especially in the right chest. Pericardial involvement could not be demonstrated. At intervals throughout the period of observation of four months, a shift of the cardiac impulse was determined with postural change. The heart-sounds were always well heard.

The sputum was repeatedly negative for acid-fast bacilli, and at no time did the X-ray studies indicate any parenchymatous involvement of the lungs, though a widened mediastinal shadow was always found.

Results from the use of tuberculin, in a dosage commonly used in testing, demand some discussion. The patient was extremely allergic, as proved by the extensive local reaction. The magnitude of the focal response was convincing evidence of the tuberculous nature of the mediastinitis. It was followed by such signs and symptoms of pressure that they were frankly alarming for some hours. Swallowing, because of oesophageal compression, was almost impossible for a time. The dyspnoea and orthopnoea were at their worst at this period. Recurrence of oedema of face, neck and upper extremities completed the picture. The patient was afebrile during the whole course until peritonitis occurred. One exception to this was about thirty-six hours following the tuberculin injection, when the temperature rose to 101°F., as evidence of a constitutional reaction.

Unfortunately Perez's (6) test was not used, whereby coarse friction sounds are elicited over the mediastinum upon the raising and lowering of the arms.

The tuberculous peritonitis, at the end of the clinical course, hardly needs discussion. It was characterized by fever, anorexia, diffuse abdominal pain, and many watery stools without tenesmus. The moderate abdominal distension, generalized tenderness without muscle rigidity, progressive loss of weight, and the continuation of symptoms until death six weeks later made the diagnosis unquestioned.

## CONCLUSIONS

1. A case of tuberculous mediastinitis has been reported, characterized by oedema of face, neck, arms and upper chest, and by progressing collateral venous circulation.

2. A widened mediastinal shadow was demonstrated by the roentgen ray.

3. Remarkable local and focal, as well as constitutional, reactions occurred following a tuberculin test.

## REFERENCES

(1) KORNBLUM, K., AND COOPER, D. A.: Tuberculous mediastinitis, Amer. Jour. Roentgenol., 1930, *23*, 276.

(2) OSLER, W.: On obliteration of the superior vena cava, Bull. Johns Hopkins Hosp., 1903, *14*, 169.

(3) HOWARD, C. P.: The diagnosis of mediastinitis, Ibid., 1915, *26*, 140.

(4) MILLES, G.: Stenosis of the superior vena cava due to mediastinal tuberculosis, Arch. Int. Med., 1932, *50*, 759.

(5) KNOX, L. C.: Chronic mediastinitis, Amer. Jour. Med. Sc., 1925, *169*, 807.

(6) PEREZ, G. B.: On a new auscultatory sign in connection with mediastinal affections, Brit. Med. Jour., 1896, *2*, 717.

# INTRAPLEURAL FIBRIN BODIES[1]

## Observations on Their Development during Pneumothorax Treatment

SAMUEL A. ROBINS AND MARK H. JORESS

Fleischner (1) in 1922 first observed discrete masses in the pleural cavity of patients receiving artificial-pneumothorax therapy for tuberculosis. By X-ray they appeared round, ovoid, pyriform, or sausage-shaped, varying in size from 0.5 cm. to 6 cm. in diameter. Although they are usually found near the diaphragm, he also noted them elsewhere in the pleural cavity. He called them "fibrin bodies." They are usually single, although several authors (Ballon (2), Klinkowstein and Belajewa (3), and Pruvost (4)) have reported multiple bodies. Auguste (5) graphically depicted the evolution of a fibrin body in a series of X-rays of the chest of one individual. During the early phases of its formation, it was suspended by a pedicle, termed the "fibrin string." Later the body became detached, giving rise to a free, mobile mass. It is this free mass which is usually observed during fluoroscopy. Zavod (6) and Wischnowitzer (7) were the first to offer histological evidence from postmortem specimens that these free, intrapleural masses consisted solely of plaques of fibrin. Brandt (8) produced them experimentally by the intrapleural injection of Scarlet-R and tar.

There has been much discussion as to the mechanism of the formation of these bodies. Fleischner (1), noting that the effusion forming in an artificial pneumothorax often contains flakes of fibrin, suggested that the fibrin body formed by a process of accretion of these flakes around an early nucleus of fibrin. This process would be facilitated by the constant motion of the exudate. Sergent and Bordet (9) believed that the plaques form only when the fibrin content of this effusion is excessively high. Dull (10) claimed that they formed from intrapleural blood clots arising from puncture of an intercostal vessel by the pneumothorax needle. He consequently called them *Blutfibrinkugel*. Poindecker (11), Stoeffel (12) and Wishnowitzer (7) suggest that the basal tip of the compressed lung, by its respiratory movements, churns the pleural

[1] From the Department of Roentgenology and the Pulmonary Clinic, Beth Israel Hospital, Boston, Massachusetts.

TABLE 1

*Analysis of the sixteen cases of fibrin bodies studied*

| NUMBER | AGE | SEX | STAGE OF DISEASE | TYPE OF COLLAPSE | DURATION OF DISEASE | DURATION OF TREATMENT | TIME OF APPEARANCE OF FLUID | AMOUNT OF FLUID | TIME OF APPEARANCE OF FIBRIN BODY | LOCATION OF FIBRIN BODY | NUMBER OF FIBRIN BODIES | SIZE OF FIBRIN BODY IN CM. | SHAPE OF FIBRIN BODY | DISAPPEARANCE OF FIBRIN BODY | LUNG TREATED | EFFECTS UPON PLEURA | CLINICAL OBSERVATIONS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 25 | M | III | Complete | ? | 3 yrs. | 2½ yrs. | Moderate | 6 mos. | Midparietal<br>Midvisceral<br>Outer diaphragm | 3 | 2.5 x 1.7<br>1.5 x 2<br>1.2 x 1 | Fusiform<br>Ovoid<br>Round | Two disappeared in 2 yrs. & 4 mos. | Right | Thickened but nonadherent | Still under treatment; moderate fluid, complete collapse |
| 2 | 23 | M | III | Complete | ? | 2 yrs. & 1 mo. | 1 yr. & 2 mos. | Slight | 11 mos. | Lung base | 1 | 1 x 2 | Ovoid | Still present | Right | Thickened nonadherent pariet. pleur. | Still under treatment; complete collapse |
| 3 | 30 | F | III | Complete | 5 yrs. | 4 yrs. & 7 mos. | 1 yr. & 1 mo. | Slight | 2 yrs. & 4 mos. | Lower portion lung at dome of diaphragm | 2 | 1.5 x 3<br>1 x 2.5 | Ovoid<br>Ovoid | 11 mos.<br>Still present | Right | Slight thickening | Still under treatment; complete collapse, basal body obscured by fluid |
| 4 | 26 | M | II | Complete | ? | 3 yrs. | 1 yr. & 2 mos. | Slight | 1 yr. | Base of lung | 1 | 1 x 1.5 | Ovoid | 3½ mos. | Left | None | Fluid still present |
| 5 | 26 | M | II | Complete | 6 yrs. | 5 yrs. | 1 yr. & 9 mos. | Slight | 3 yrs. & 9 mos. | Parietal pleura suspended by pedicle | 1 | 3 x 5 | Pear | Still present | Right | Slight thickening | Fluid gone; complete collapse |
| 6 | 24 | M | II | Complete | 6 yrs. | 5 yrs. | 4 yrs. & 8 mos. | Slight | 2 yrs. | Base | 1 | Cherry stone | Round | Still present | Left | None | Fibrin body present at end of treatment period (5 yrs.) |
| 7 | 19 | M | III | Partial | 4 yrs. | 2 yrs. | ? | Slight | 1 yr. | Outer portion of diaphragm | 1 | 1 x 1.5 | Ovoid | ? | Right | None | Patient died |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 21 | F | III | Partial | 3 yrs. | 1 yr. | 11 mos. | Slight | 8 mos. | Dome of diaphragm | 1 | 1.5 x 2 | Ovoid | ? | Right | None | Patient died |
| 9 | 42 | F | III | Complete | 7 yrs. | 6 yrs. | ? | Slight | 3 yrs. | Dome of diaphragm | 1 | 2 x 2.5 | Ovoid | 1 yr. | Left | None | Lung being reëx-panded after 6 yrs. collapse; clinically well |
| 10 | 36 | M | III | Partial | 6 yrs. | 5 yrs. | 4 yrs. & 8 mos. | Slight | 1 yr. | Dome of diaphragm | 1 | 1 x 1.5 | Ovoid | 16 mos. | Right | None | Pneumothorax aban-doned, reactivation contralateral lung |
| 11 | 23 | M | II | Complete | 3 yrs. | 3 yrs. | ? | Slight | 1 yr. | Periphery lower lobe | 1 | 3.5 x 2.5 | Pear | 1 yr. | Right | Thickening | Homolateral reacti-vation at end of treatment period |
| 12 | 30 | M | III | Complete | 5½ yrs. | 3 yrs. | ? | Slight | 1 yr. & 9 mos. | Base of upper lobe | 1 | 1.5 x 2.5 | Pear | 1 yr. & 2 mos. | Left | Thickening | Still under treatment —well |
| 13 | 25 | M | III | Complete | 5 yrs. | 5 yrs. | 1 yr. & 8 mos. | Slight | 10 mos. | Base lung, lateral border upper lobe | 2 | 3 x 3.5<br>1.5 x 3 | Spherical<br>Pear | 8 mos. | Left | None | Still under treatment —well |
| 14 | 25 | M | III | Complete | 6 yrs. | 4 yrs. | 2 yrs. & 6 mos. | Moder-ate | 2 mos. | Periphery of mid-lung | 3 | Small | Sausage | Persists | Left | Slight thickening | Still under treatment —good condition |
| 15 | 32 | F | III | Complete | 5 yrs. | 5 yrs. | 2 yrs. | Slight | 3 mos. | Periphery of lung lower lobe | 1 | 1.5 x 1.5 | Spherical | 2 yrs. & 3 mos. | Left | None | Still under treatment —well |
| 16 | 55 | M | III | Partial | 8 yrs. | 2 yrs. & 6 mos. | 2 mos. | Slight | 2 mos. | Periphery lower lobe & inner por-tion diaphragm | 1 | 3 x 3.5 | Pear | 2 yrs. | Right | Pleural thickening | Treatment stopped contralateral reac-tivation |

effusion. In drawing away from the fluid, this lobe then develops a fibrin string which eventually breaks off and forms a free fibrin mass in the pleural cavity. Other theories of the aetiology of fibrin bodies are: cellular proliferation of the pleura, preëxisting masses of false pleural membrane which have become detached, and inflammatory products which are converted into fibrin masses. These theories are not now entertained seriously by most observers.

There is now general agreement that the presence of effusion is a prerequisite for the formation of fibrin bodies; that they appear especially during the stages of beginning resolution and organization of the exudate; and that their development requires that the fluid be especially rich in fibrin.

In a series of seventy-five patients receiving artificial-pneumothorax therapy, we have made a special study of the formation of fibrin bodies. Sixteen of these patients showed such fibrin bodies. A pleural effusion had been present in all these sixteen patients and in five the volume had been sufficient to obscure the diaphragm and the costophrenic angle. The fibrin body may form during the early stages of development of the pleural exudate, but rarely can be visualized until the phase of absorption of fluid begins. It was only by repeated search during this phase of their evolution that we have observed fibrin bodies in sixteen out of seventy-five patients, an incidence of 21 per cent. (See table 1.)

The fibrin bodies were usually pyriform or spheroidal and were most often located near the dome of the diaphragm. They were usually single. However, as many as eight bodies have been observed by one of us (M.H.J.).[2] Incipient fibrin bodies, "young forms," were observed as small, comma-shaped masses attached to the pleural surface of the compressed lung. We believe that these young forms are the nuclei for the later development of the large, mature body in the presence of an excessive amount of fibrin in the exudate. These large bodies ultimately

FIG. 1a. Arrows point to fibrin bodies attached to region of mediastinum ("young form"). Small exudate present.

FIG. 1b. These bodies are not seen; obviously they are hidden by the fluid which has increased.

FIG. 2. A case of multiple fibrin bodies observed by one of us (M. H. J.) through the courtesy of Dr. H. F. R. Watts.

FIG. 3a. Beginning of a fibrin body. It is seen in relation to diaphragmatic contour.

FIG. 3b. Later stage in its development; note its position between diaphragm and lower end of lung.

[2] Through the courtesy of Dr. H. F. R. Watts of Boston.

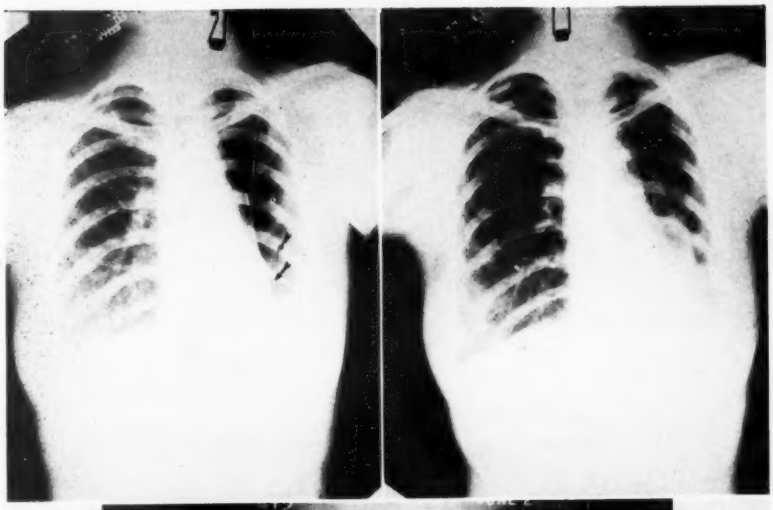


FIG. 1a

FIG. 1b

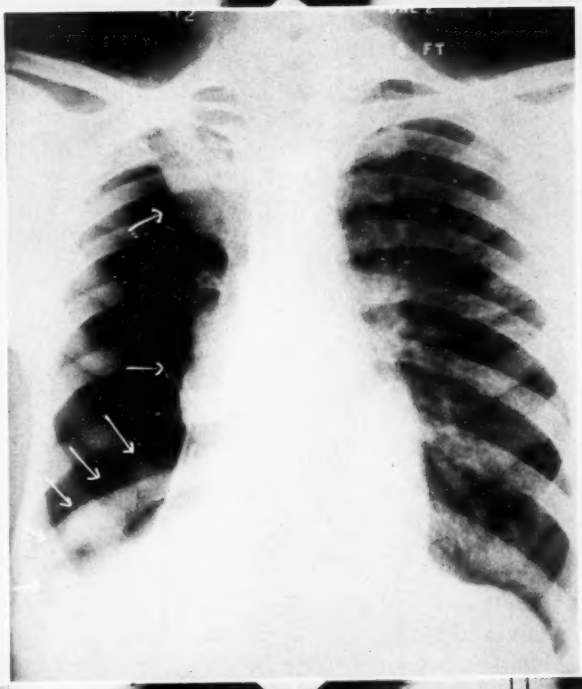



FIG. 2

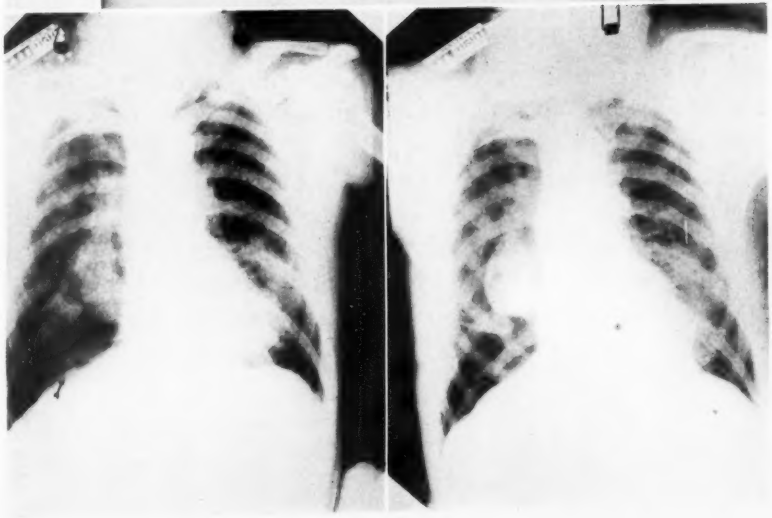


FIG. 3a

FIG. 3b

disappear. However, even after the effusion has become completely resorbed, or has become organized, a shadowy outline of the mass may remain for a long time. Fibrin bodies were never noted after reëxpansion of the lung following cessation of treatment.

The earliest appearance of these bodies was thirteen months and the latest seven years following the institution of pneumothorax therapy. The average period for the first appearance of the fibrin body was four

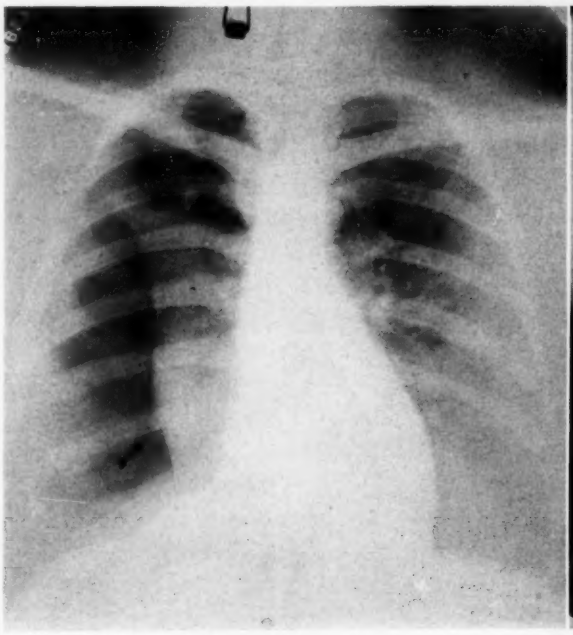


FIG. 4

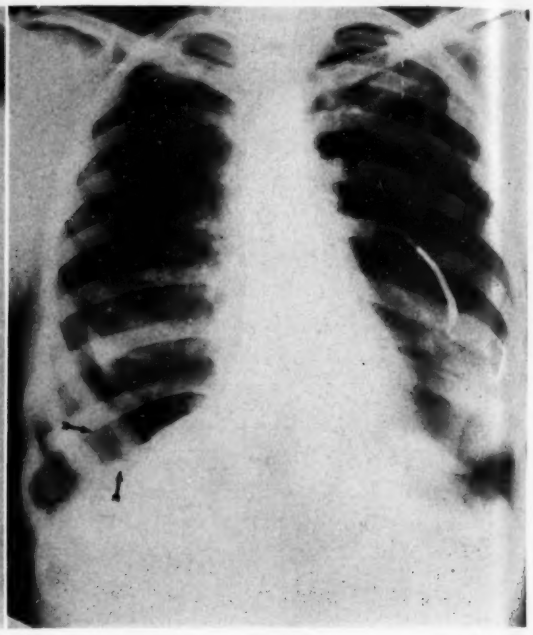


FIG. 5

FIG. 4. Arrow points to a fibrin body attached to lower edge of compressed lung.

FIG. 5. Lower arrow points to a large fibrin body lying unattached in pleural cavity; upper two arrows point to a body closely attached to the lower portion of the lung.

and one-half years. Although the sexes are equally divided in the total series, of the sixteen cases developing fibrin bodies, twelve were males and four females.

As a rule patients are not aware of the presence of these bodies. Occasionally, however, they describe a sensation of something striking against the chest-wall as they assume different positions. In some cases they remain for long periods either occupying their original position attached to the margin of the compressed lung, or they may become de-

tached and remain as loose bodies in the pneumothorax cavity. Their shape may be changed from time to time, depending upon the degree of expansion of the lung.

## REFERENCES

(1) Fleischner, F.: Kugelförmige Gebilde in der Pleurahöhle bei Pneumothorax, Mitt. d. Ges. f. inn. Med. u Kinderh. in Wien, 1922, *21*, 94.
(2) Ballon, H. C.: Fibrin body in pneumothorax cavity, Amer. Jour. Roentgenol., 1929, *22*, 234.
(3) Klinkowstein, J., and Belajewa, N.: Fibrinkugeln im Pneumothoraxraum, Beitr. Klin. Tuberk., 1926, *58*, 313.
(4) Pruvost, P.: Lepennetier, F., and Meyer, A.: Corps libre intrapleural, Arch. Med. Chir. l'App. Resp., 1931, *6*, 247.
(5) Auguste, C.: Sur la formation de corps fibrineux dans la cavité du pneumothorax artificiel, Rev. de la Tuberc., Paris, no. 8, 821.
(6) Zavod, W. A.: Fibrin bodies in the pleural space in a case of artificial pneumothorax, Amer. Rev. Tuberc., 1936, *33*, 48.
(7) Wischnowitzer, L.: Fibrinkörper im Pneumothoraxraum, Beitr. Klin. Tuberk., 1927, *57*, 773.
(8) Brandt, M.: Ueber freie Körper im Pleuraraum, Virchow's Arch. f. path. Anat., 1927, *258*, 574.
(9) Quoted by Auguste in ref. 5.
(10) Dull, W.: Vorkommen von "Blut—Fibrinkugeln im Pneumothoraxraum," Beitr. Klin. Tuberk., 1924–1925, *60*, 307.
(11) Quoted by Auguste in ref. 5.
(12) Quoted by Auguste in ref. 3.

# HAEMORRHAGE IN PULMONARY TUBERCULOSIS[1]

CHARLES K. McCARTHY

The expectoration of blood may be a symptom of any one of several diseases. It is practically always a symptom of some serious condition. In cases wherein it is the initial symptom, extensive and careful study must be made in order to arrive at an early and correct diagnosis.

A careful history is all-important. It will frequently give a lead. It is indispensable in cases far removed from X-ray facilities. It is surprising to find how many patients suffering from this symptom will give a history of undue fatigue, or slight loss of weight many months before the haemorrhage occurred. Such a history points immediately to the chest as the site of the trouble.

On the other hand a complaint of vague or perhaps severe pain in the epigastrium, unexplained attacks of nausea, vomiting, diarrhoea or constipation, suggest that the trouble is probably to be found in the abdominal cavity, although the chest may be involved also. A history of alcoholism is very suggestive. But at no time is a haphazard history justified, for ninety-nine times out of a hundred a thorough history gives one or several definite clues.

While there may be several causes for expectorating blood, many internists are of the opinion that all haemoptyses should be considered as due to pulmonary tuberculosis until proved otherwise. An X-ray film of the chest, as well as a careful physical examination, is always indicated as soon as possible. In the majority of cases the seat of the lesion will be found there.

The patient with pulmonary tuberculosis, whose initial symptom is haemoptysis is fortunate. The sight of blood drives him to the doctor much faster than any other symptom would. He thus receives the benefits of earlier diagnosis and treatment than he otherwise would.

The primary purpose of this paper is to discuss haemoptysis in tuberculosis. However, this necessarily involves discussing, to some extent, the cases of bronchiectasis, lung abscess and neoplasm, which drift into sanatoria.

[1] From the Rutland State Sanatorium, Rutland, Massachusetts.

I have taken one thousand consecutive cases from our records, which, I think, give a fair cross-section of the general run of patients. Our patients are all over seventeen years of age.

We admit several cases each year, and see numerous other ones in our out-patient department, in which haemoptysis has been the initial, or an outstanding symptom. In many of these it is difficult to make a definite diagnosis until after a period of extensive study. Not infrequently a case admitted with a diagnosis of pulmonary tuberculosis proves eventually to be something else.

There are several possible explanations for haemoptysis. Diapedesis, changes in temperature, engorgement of vessels, such as occurs at the time of menstrual periods, a decrease in antithrombin in the blood, are some of the theories which have been advanced.

For all practical purposes one cause may safely be assumed as the only one of consequence, namely erosion of a blood vessel. Whether this be due to tubercle bacilli or to other microörganisms makes little difference except insofar as it may direct treatment. From the standpoint of treatment, it is extremely important that no mistake be made as to why the patient is expectorating blood. In cases which reveal clear apices one must consider bronchiectasis and abscess. The more extensive use of lipiodol has shortened, considerably, the period of study necessary for making a correct diagnosis. Some of the most profuse haemorrhages are seen in pulmonary abscess, and bronchiectasis.

Because of modern advances in chest surgery, it is extremely important to rule out pulmonary tuberculosis. Lobectomy, definitely contraindicated in pulmonary tuberculosis, is to-day curing other pulmonary diseases which were formerly considered hopeless.

*Frequency of haemoptysis:* The frequency of haemoptysis in pulmonary tuberculosis is still a debated question. The figures in the literature vary from as low as 20 per cent. to as high as 80 per cent.

In the one thousand cases studied 40.4 per cent of patients had one or more haemoptyses during the course of the disease.

Some writers speak of a seasonal element. In a study of 408 episodes of haemoptyses, the monthly distribution did not reveal any evidence for a seasonal factor.

*Prophylaxis of haemoptysis:* It has been generally accepted that overexertion plays an important part in bringing on pulmonary haemorrhage. It is interesting to note, however, that the greater number of our cases occur among patients who are spending practically twenty-four hours a

day in bed. Furthermore, they usually occur at night, frequently waking the patient from a sound sleep. This is true not only in the frankly active patient, but as well in expatients who work all day.

However, we find exceptions to this rule. Recently I examined a patient who had had a thoracoplasty six months previously. I saw this patient in the early evening, six hours after she had been tripped by a dog and had fallen down a flight of stairs. A few minutes after the fall she had had a haemoptysis of several mouthfuls. After the bleeding stopped she rode sixty miles by bus to the Sanatorium. She expectorated no more blood and had not even streaked sputum.

*Treatment:* The treatment of haemoptysis in pulmonary tuberculosis is unsatisfactory. Fortunately most haemorrhages cease spontaneously. One can never be certain whether the treatment or nature has caused the haemorrhage to cease. Haemorrhages may be fatal before treatment can even be begun.

Bed-rest is essential in the treatment of haemorrhage. Because the patient is always greatly alarmed, he must have mental as well as physical rest. Consequently sedatives must be used. Morphia, barbital, luminal, dilaudid, in fact practically any sedative is efficient in allaying nervousness, but should never be used to the point of abolishing the cough reflex.

Nitroglycerine and ice-caps to the chest may be used in an attempt to lower blood-pressure. Calcium lactate, calcium chloride, and sodium chloride by mouth, have been used in an effort to hasten the coagulation time. We have also used thromboplastin, both intramuscularly and intravenously. Congo-red has also been tried. However, it is the consensus of the medical staff that we have no definite criteria as to the efficacy of any of these measures.

It is interesting to note, however, that the most severe haemoptysis that we have seen at this Sanatorium in several years (ninety-six ounces in three days) stopped finally after several intravenous injections of thromboplastin. This patient was practically moribund. He lived sixteen months after the cessation of that haemorrhage and had but one dram of blood thereafter. His X-ray film showed numerous large cavitations in both lungs.

When a haemoptysis occurs the patient appreciates anything that is done. He is always terribly alarmed and is always convinced that the treatment, whatever it may be, has stopped the bleeding. I have been told repeatedly afterwards how pleased the patients have been to have so much done for them while they were bleeding.

We have found collapse therapy extremely important in the control of bleeding. We believe that artificial pneumothorax, instituted in the suitable case, has frequently collapsed a lung sufficiently to control haemorrhage.

I have a patient at the present time, who had bled intermittently for a week, several ounces a day, before admission, as well as during the first few days after admission. Artificial pneumothorax was begun immediately. She only bled once after collapse was instituted. We have not been so successful in the use of artificial pneumothorax as an emergency method in large haemorrhages. One difficulty is that it is not always possible to be sure from which side the blood is coming. In cases with extensive lesions with a tendency to bleed pneumothorax has usually been tried already and found to be impossible.

We have had some success in the above type of case with phrenic nerve paralysis.

We have frequently and with considerable success resorted to thoracoplasty in order to arrest periodic haemoptysis.

*Prognosis:* The question as to whether haemoptysis occurring in the course of pulmonary tuberculosis changes the prognosis for the worse is sometimes debated. We have noted several cases in which occasional small haemoptyses have appeared to make no difference in the course of the disease. We have among our employees a large percentage of former patients. Many of these people have an occasional small haemorrhage. Usually a few days in bed is all that is necessary to get them back on the usual routine. Apparently there are no harmful effects.

However, there are many other cases in which a haemorrhage, large or small, definitely marks the beginning of a downhill course. It frequently results in a marked increase in the lesions in one or both lungs. In this series of one thousand cases, there were 179 deaths, a percentage of 17.9, which were definitely the result of haemorrhage. There were 93 deaths, 9.3 per cent, among the cases who had never had a haemoptysis.

## CONCLUSIONS

1. The expectoration of blood demands careful study so that a correct diagnosis may be made before treatment is instituted.

2. Sedatives are essential to allay nervousness, but the value of substances used to lower blood-pressure or hasten coagulation of blood is questionable.

3. Collapse therapy is indicated, wherever possible, for the control of pulmonary bleeding in tuberculosis.

4. The importance of overexertion in bringing on pulmonary haemorrhage is debatable.

5. The seasonal factor in the occurrence of haemoptysis is unimportant.

6. The prognosis is definitely graver following haemoptysis in most cases of pulmonary tuberculosis.

# THE COURSE OF EXPERIMENTAL PNEUMOCOCCUS INFECTION IN TUBERCULOUS RABBITS[1]

J. WEISSFEILER, E. N. MOROZOVA AND A. I. STRUKOV

In the course of a prolonged tuberculous infection, acute infectious diseases frequently occur. In such cases the two processes influence each other in two directions. First, the acute infection can alter the further course of the tuberculosis and second, the course of the secondary infection in the tuberculous organism varies from that in a healthy organism.

Koch was the first to point out the significance of secondary infections in tuberculosis. Since, many studies (Spengler, Petruschky, Courmont, Chmelnitsky) have been devoted to this subject. The second problem, the course of a secondary infection in the tuberculous organism, has received less attention. In practice, this question arose a long time ago in the following formulation: Can a tuberculous organism react to an acute infection as well as a healthy one, or does the course of the acute infection take a more serious course? It might be expected that an infected organism would cope with the secondary infection with greater difficulty than the healthy one. However, clinical observation showed that many acute infections are borne by tuberculous patients with no more difficulty than by nontuberculous patients; but the tuberculous process may be aggravated by acute infections.

Most of the acute diseases of the lungs are caused by pneumococci. Therefore the problem of pneumococcus infection during tuberculosis of the lungs is of great significance. That pneumococcus infection aggravates the course of tuberculosis of the lungs has been shown by Courmont and Boissel, as well as by Stefko. On the other hand, Fränkel, Schröder and others found that lobar pneumonia in patients with tuberculosis is a rather rare occurrence and that its course is not more serious than in the nontuberculous. At autopsy, pneumonia has very rarely been found to be the cause of death in tuberculosis patients (Stefko).

Experimental researches of the last few years have also shown that

[1] From the Central Institute for Tuberculosis, Moscow.

tuberculous animals bear some acute infections not worse and sometimes even better than healthy ones. The tissue processes, on which these observations are based, have however not been studied. Weissfeiler found that the reaction to a subcutaneous infection with staphylococci is modified by a coexistent tuberculosis. The influence that tuberculosis exerts on a nonspecific infection is termed heteroallergy.

Rössle's pathergy and Moro's parallergy are probably phenomena of the same order as Weissfeiler's heteroallergy. Pagel also established the difference in the reaction of the healthy and tuberculous guinea pig, following the injection of sanocrysin. He reported detailed histological studies.

Bieling and Oelrichs studied experimental pneumococcus infection in tuberculous animals. They observed that tuberculous rabbits react to intratracheal pneumococcus infection more violently than healthy ones. However, the infiltration formed after inoculation of pneumococci vanishes quicker in tuberculous than in healthy animals. These experiments show that intratracheal pneumococcus infection causes the same heteroallergic reaction in the lung tissue of tuberculous animals that Weissfeiler observed in staphylococcus infection of the skin—violent but quickly vanishing responses and necrosis of the tissue. The same local reaction is observed in the lung of a tuberculous organism as in the skin. An entirely different situation is observed during the course of a secondary infection following intravenous inoculation, since in this case the injected bacilli enter directly into all the organs. The reaction which follows is not limited to the site of injection as it is in subcutaneous or intratracheal inoculations; it is a general reaction.

In the case of intravenous infections we must formulate the question in the following way: How is the heteroallergic alteration expressed during the general infection of the organism? In peritoneal infection we have a large surface which reacts to the injected microörganisms, and the peritoneum reacts as an absorbing organ, which distributes the microbes by means of phagocytes throughout the organism and, therefore, the latter reacts in the same way as in intravenous inoculation.

In view of this we studied the course of experimental pneumococcus infection after intravenous and intraperitoneal inoculation of tuberculous and healthy rabbits. We were interested in the following questions: (*1*) Is the outcome of the infection in a tuberculous animal more or less favorable than in a healthy one? (*2*) What are the histological differences in the reaction of the healthy and tuberculous organism?

## DESCRIPTION OF THE EXPERIMENTS

Our experiments were done on rabbits, which had received an intratracheal inoculation of virulent bovine tubercle bacilli in a dose of 0.1 mgm. two months previously. They had far advanced tuberculosis of the lungs. These rabbits were infected with pneumococcus type I which, when introduced in a dose of 0.25 to 1 cc. in some intraperitoneally and in some intravenously, usually killed healthy rabbits. Simultaneously, the healthy control animals were infected with pneumococcus in the same way as the tuberculous ones. Besides this, tuberculous rabbits not infected with pneumococcus were killed in order to have material for comparative histological study.

Altogether 14 tuberculous and 13 healthy rabbits were used. Seven rabbits were infected with pneumococcus intraperitoneally, and 7 intravenously. Upon studying the mortality of animals following infection with pneumococcus, we found no definite difference between the two groups of animals. Among the healthy, as well as among the tuberculous rabbits, 7 died after 24 hours, and 3 animals of each group lived longer than five days, and had no longer any pneumococci in their blood. The rest of the animals died between two to four days following the infection with pneumococcus. Thus, tuberculous animals showed the same resistance to pneumococcus as the healthy ones. At the same time, the method of inoculating pneumococcus had no significance for the outcome of the infection. Histological study of the organs was done by A. I. Strukov. He studied the lungs, liver, spleen, kidneys and, in certain cases, the heart. A sharp difference in the reaction of the lungs of healthy and tuberculous animals was established, and therefore the main attention was devoted to this organ. Protocols of the healthy and tuberculous animals who died or were killed following one, three and fifteen days show this difference.

## DISCUSSION OF THE RESULTS

The fact that the course of pneumococcic infection in the tuberculous organism is not more serious than in the healthy one deserves particular attention. All animals without exception had a serious form of tuberculosis of the lungs. This would indicate that even progressive tuberculosis does not lower the resistance against secondary infection with pneumococcus. The question of whether this identical resistance is the result of similar reactive capacity in healthy and tuberculosis animals was studied histologically.

FIG. 1

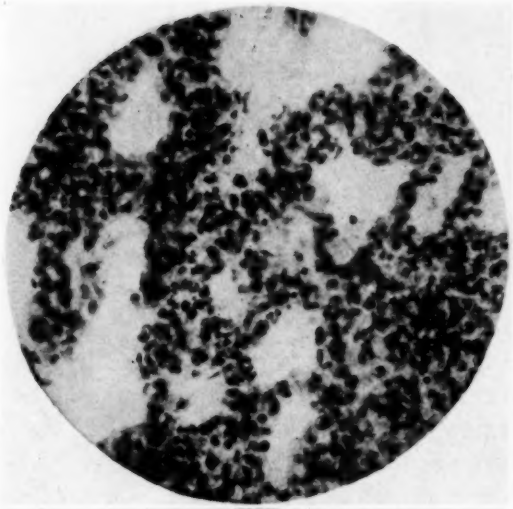
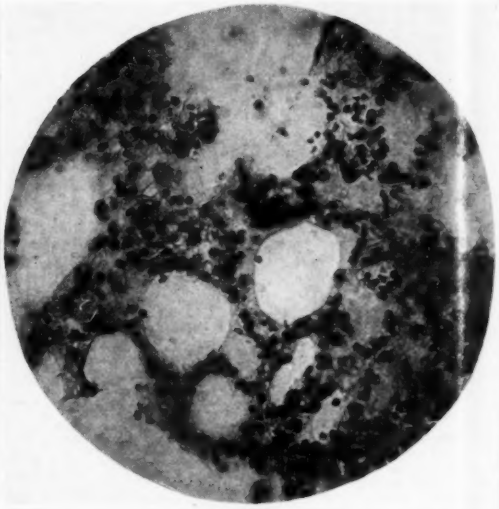


FIG. 2



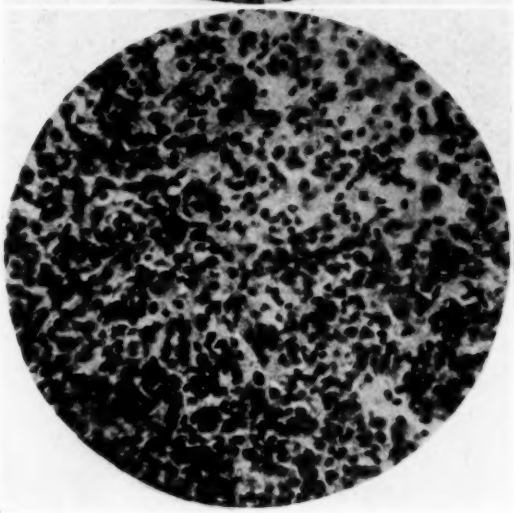


FIG. 3

FIG. 4

FIG. 1. Control rabbit. Lung, 24 hours following infection with pneumococci. Interstitial pneumonia.

FIG. 2. Tuberculous rabbit. Lung, 24 hours following infection with pneumococci. Slight thickening of the alveolar walls.

FIG. 3. Control rabbit. Lung, 15 days following infection with pneumococci. Abscess formation.

FIG. 4. Tuberculous rabbit. Lung, 14 days following infection with pneumococci. Desquamative pneumonia.

Following intravenous inoculation of pneumococcus in tuberculous and healthy animals a different reaction results in the lung tissue. Intravenous injection of 0.5 cc. of pneumococcus broth causes in healthy animals a clear-cut interstitial pneumonia on the first day. The alveolar partitions become thickly infiltrated with cellular elements among which leucocytes and histiocytes are found. In tuberculous animals the same dose of pneumococcus causes only oedema of the alveolar walls, hyperaemia and a slight proliferation of histiocytes. A similar picture was observed with smaller doses. In those healthy animals which lived for 15 days, desquamative pneumonia and abscess formation were noted, while tuberculous animals developed a desquamative pneumonia in a considerably lighter form.

Following intraperitoneal inoculation of pneumococcus the reaction of the lung tissue was considerably slighter than following intravenous administration; however, a more acute thickening of the interalveolar partitions was observed in the nontuberculous animals. In the liver of the healthy as well as of the tuberculous animals some fatty degeneration could be observed, and cellular proliferation in the periportal tissue. In the majority of tuberculous animals, miliary necroses were observed in the liver in addition to fatty degeneration.

In the spleen acute hyperaemia developed and miliary necroses in the tuberculous animals.

No difference in the reaction of the kidneys could be observed in the two groups. Degenerative changes in the epithelium of the ducts were noted in both groups.

Interstitial processes in the heart of the healthy animals are more frequent than in the tuberculous animals under similar conditions.

An analysis of the histological changes in the organs of the healthy and tuberculous animals shows that the cellular reactions in the healthy rabbits are considerably slighter than those in the tuberculous animals. This difference is particularly clearly seen in the lungs. In the parenchymatous organs, interstitial reactions predominate in the healthy animals, while in tuberculous rabbits mainly degenerative processes are noted resulting in necrosis.

Thus, we see a clear-cut difference in the reaction to pneumococcus of healthy and tuberculous rabbits. A higher degree of activity of the reticuloendothelial system is observed in tuberculous animals. This is manifested by less intense inflammatory processes and by a greater tendency to necrosis. Our observations in many ways coincide with those of

Pagel, who also observed a prolonged reaction of the reticuloendothelial system in tuberculous guinea pigs after introduction of sanocrysin; by this the author tries to explain the interesting fact that tuberculous animals can survive a multiple of the dose of sanocrysin fatal to nontuberculous animals.

However, is there any possibility to conciliate the results of our observations with Weissfeiler's observations following subcutaneous infections with staphylococcus and with those of Bieling and Oelrichs following intratracheal infection with pneumococcus? In the works mentioned above a stronger reaction in a tuberculous organism than in a healthy one was observed; but we have observed in our work directly opposite occurrences. In all probability, the cause of this difference lies in the fact that in the studies quoted above local infection occurred, while in our experiments we produced general infections. In future experiments it will be necessary to discover whether the reaction is the same in animals less affected with tuberculosis and infected with pneumococcus by methods closer to natural conditions.

Our observations have therefore added new material to the explanation of the mechanism of heteroallergy in a tuberculous organism. This mechanism is not always the same, sometimes it is manifested by a more acute and sometimes by a more prolonged cellular reaction. Although it has not yet been discovered under what conditions that or other forms of heteroallergy occur, certain points of departure for solving this question have been established by us.

## SUMMARY

1. Rabbits infected intratracheally with virulent strains of tubercle bacilli of bovine type cope with an intravenous or intraperitoneal inoculation of pneumococcus, type I, as well as control animals: out of 14 tuberculous animals 7 died within 24 hours; out of 13 control rabbits, 7 also died. Three tuberculous and three healthy control animals lived for a period longer than 4 days.

2. The cellular reaction in a tuberculous animal clearly differs from that in a healthy rabbit. The reaction of tuberculous animals takes a slower course, has a more exudative character and tends more toward necroses than the reaction of healthy rabbits.

3. The difference observed in the reactions of tuberculous and healthy animals can be explained by heteroallergy due to tuberculous infection. Thus, heteroallergy plays an important part in the course of nonspecific infectious processes in a tuberculous organism.

## REFERENCES

BRAUER AND PETERS: Handbuch d. Tuberk., 1923, Bd. 2.
BIELING: Medizin u. Chemie, 1934, Bd. 2, p. 76.
BIELING AND OELRICHS: Ztschr. f. Tuberk., 1934, *59*, 242.
CHMELNITSKY: Žurn. eksperim. biol. i. medic., 1926, p. 123; Vratschebn. dielo, 1926, no. 5–6.
COURMONT AND BOISSEL: Jour. de Méd. de Lyon, October 20, 1925.
MORO: Monatschr. f. Kinderheilk., 1926, *34*, 193.
PAGEL: Krankheitsforschg., 1926, *3*, 372.
PETRUSCHKY: Beitr. Klin. Tuberk., 1923, *62*, 43.
RÖSSLE: Wien. Klin. Wchnschr., 1932, *1*, 609.
SCHRÖDER: Handbuch. d. Tuberk., 1923, Bd. 2.
SPENGLER: Zentralbl. Bakt., 1901, *30*.
WEISSFEILER: Ztschr. f. Immunitätsforsch., 1934, *83*, 203; Amer. Rev. Tuberc., 1935, *32*, 719.
SUPINO: Giorn. Batteriol., 1935, *14*, 1457.
MENKIN: Jour. Exper. Med., 1932, *56*, 157; 1933, *57*, 977.

# Henry Robert Murray Landis
## 1872–1937

Henry Robert Murray Landis died of tuberculosis in the Bryn Mawr Hospital on September 14, 1937. His illness had been a long one, the disease having been manifest first while he was an interne in the Philadelphia General Hospital in 1899. His health was apparently restored at Saranac Lake, where he knew intimately the able and distinguished staff of Trudeau Sanatorium. His life was much influenced by these early contacts, and was an example of Dr. Trudeau's greatest achievement, the inspiration he transmitted to those who knew him to devote their lives to the campaign against tuberculosis. Dr. Landis worked in this field for thirty-five years after his breakdown with splendid courage and recognized success.

He was born in Niles, Ohio, on February 3, 1872. His father was a member of the Landis family of Pennsylvania, which had produced a number of prominent and successful men. At Amherst College, where he was graduated in 1894, his course was marked by fair scholarship and great devotion to baseball. He was always loyal to Amherst and the friends he made there; he was very proud of the number of Amherst men who have rendered conspicuous service to the country; and the receipt of the degree of Doctor of Science from his alma mater in 1929 was to him the crowning honor of his life. His medical training was taken at the Jefferson Medical College in Philadelphia, from which he graduated in 1897.

In 1902, he married Miss Margaret Tucker of Philadelphia, who survives him.

His active medical life was devoted to the study and prevention of tuberculosis. His return to work after his first temporary restoration to health was coincident with the founding of the Henry Phipps Institute under Dr. Lawrence F. Flick as Director. Dr. Landis became a member of its staff and later was made Director of the Clinical and Sociological Departments, which office he still held at the time of his death. In 1926, he was made Professor of Clinical Medicine in the University of Pennsylvania. Although his work was chiefly in the field

of tuberculosis, his knowledge of general medicine was very wide. He was the editor of International Clinics from March, 1916, until June, 1921. During the World War he was for a time Acting Physician-in-Chief of the Peter Bent Brigham Hospital in Boston.

Henry Robert Murray Landis
1872–1937

He was the author of many papers dealing with tuberculosis. His textbook *Diseases of the Chest*, written in collaboration with Dr. George W. Norris, was first published in 1917 and has gone through five editions. It still is the most widely used textbook dealing with this field in many of the medical schools of the country. He was on the Editorial Board of the AMERICAN REVIEW OF TUBERCULOSIS.

During his first decade at the Henry Phipps Institute, Dr. Landis

made studies in interesting fields connected with conditions he found among his clinic patients. He supervised a study of working conditions in the clothing industry; he was a pioneer in organizing a business in which rehabilitation of patients who had improved under treatment could be carried on; he devised a system by which studies of tuberculosis in the Negro race could be conducted by Negro doctors and nurses under his training and supervision. He was a member of the visiting staff of the White Haven Sanatorium for more than thirty years, and, while on this duty, became greatly interested in the manifestations of disease caused by dust inhalation. His papers on silicosis and anthracosis are among the pioneer studies in this field.

In his own thought, his study of tuberculosis in the Negro race and the development of Negro work was his most interesting and constructive accomplishment. It originated in his perception, during his early years at the Institute, that Negro patients were few in proportion to the total attendance, and that many of them made only one visit. He felt that white doctors and nurses perhaps did not understand the workings of the Negro mind, its fears, superstitions, dislikes, etc. Accordingly, in 1914, he added to the staff, through financial assistance from the Whittier Centre of Philadelphia, a competent Negro nurse. This experiment was a pronounced success, as Negro patients came to the clinic in constantly increasing numbers and continued their treatment. When the Negro Bureau of the Philadelphia Health Council and Tuberculosis Committee was formed, Dr. Landis was made Chairman, and the Negro staff under his supervision numbered ten physicians and twelve nurses. In succeeding years his method of dealing with this problem has had a very wide influence, not only in Philadelphia, but throughout the nation. This is shown by the recent report of the Committee of the National Tuberculosis Association on Tuberculosis in the Negro, of which Committee he was Chairman.

Dr. Landis was one of the founders of the National Tuberculosis Association, and an Honorary Vice-President during the last three years. He was President of the Pennsylvania Tuberculosis Society from 1928 to 1932, and for years was an influential member of the Board of Directors of the Philadelphia Health Council and Tuberculosis Committee. Among the many societies in which he took an active part were the College of Physicians of Philadelphia, the National Tuberculosis Association, the Association of American Physicians, the American

Sanatorium Association, the American Clinical and Climatological Association and the American Medical Association.

Dr. Landis, in addition to his medical interests, was a man of broad scholarship and wide reading. He was a collector of rare books and prints. His attractive and forceful personality made him an inspiring teacher and an interesting companion. His friendships in social life and in his clubs were very wide. He was of aristocratic tastes, but perhaps his most strongly marked characteristic, showing the heart of the man, was his friendly attitude toward his subordinates in all hospital, clinic, club and domestic relationships. This is shown by an incident which became known just after his death. Among his papers there was found a pencilled note written in the hospital, in which he requested that the services at his funeral should be in his home, simple and private, only the family and close friends to be present, except that every member of the staff and employees at the Institute, white and black, should be invited to attend.

Bob, or "Hiram," as he was known, is greatly missed by his many friends. Their sorrow at his death need not be described here.

C. J. H.

## BOOKS

CUMULATIVE INDEX OF THE AMERICAN REVIEW OF TUBERCULOSIS, *Volume I to Volume XXXIV, March 1917–December 1936. Pp. 211, National Tuberculosis Association, New York, May, 1937, cloth, $2.50.*

The first Cumulative Index of the American Review of Tuberculosis contains all original papers that appeared in the first thirty-four volumes, indexed and carefully cross-indexed according to subjects and authors. This work is based mainly on the volume indices most of which were prepared with painstaking accuracy by the Editor, Dr. Allen K. Krause. Without this basic work, the preparation of the cumulative index would have required an amount of labor and time that would probably have multiplied its price. This 211 page volume is not only the helpful working instrument that every cumulative index is; it is at the same time a record of the scientific management of the Review from March, 1917 on, and it is a representative summary of the tuberculosis work in this country during the last twenty years.

One might well browse through this volume, in spite of the apparent aridity of an index, and one may extract from it interesting information as to the trend of the published work, as to its distribution in the various fields of endeavor. It would seem significant, for example, that the references under *Pathology* cover barely more than one column whereas *Experimental* heads about four columns and *Tubercle Bacillus* eight and a half. It may come as a surprise to find that in the first five volumes there were published almost as many papers on artificial pneumothorax as in the last five volumes. On the other hand, only fourteen papers on intrathoracic malignancies have been published, all of them, with the exception of four, from volume XXI on.

The main purpose of these lines is, however, to emphasize that this Cumulative Index is most useful to anyone doing bibliographic work in the field of tuberculosis.

WILLIAM F. PETERSEN: *The Patient and the Weather, Volume IV, Part 2, Organic Disease (Hypo and Hyperthyroidism, Diabetes, the Blood Dyscrasias, Tuberculosis), with the assistance of Margaret E. Milliken. Pp. xvi + 729, with 380 figures in the text, lithoprinted by Edwards Brothers, Inc., Ann Arbor, Michigan, 1937, $11.00.*

*By* AARON E. MARGULIS

"We are imitative beings; we respond to the tone and colour of our environment almost against ourselves, and still have our links with the chameleon and the moth."

—JAMES STEPHENS, *The DemiGods.*

This review will attempt only to delineate the scope of this book rather than essay a complete description and critical analysis of its contents. First, the subject of tuberculosis occupies only a minor part of this volume (the remainder treats of thyroid disorders, blood dyscrasias, and diabetes), a subsequent comprehensive monograph devoted to tuberculosis being promised. Second, an abstract necessarily brief to meet the requirements of the Review would be unfair to the author and misleading to the prospective reader, for just as this work embodies a synthesis, so does it gain in totality and lose in dissection. The whole imparts a significance and a satisfactoriness that is only dimly perceived in a summary of it.

This volume is an additional unit in Doctor Petersen's prodigious study which may be tentatively catalogued as a treatise on human ecology, although, as will be shown, its final aim has deeper and broader implications than that designation implies. It is a continuation of the study of adaptation that has its roots in Darwinism—a study, as Doctor Petersen emphasizes, in purely materialistic terms, of Darwinian fitness as compounded of the mutual relationship between organism and environment.

Of the many environmental factors involved in this relationship Doctor Petersen's concern lies with those that are commonly grouped under the term "weather." He has attempted to establish the general thesis that meteorological changes are of significance for, and may initiate disease processes, or precipitate episodes in their evolution. The average reaction to this thesis, the reviewer has discovered for himself, is one of scepticism or derision. An analysis of this illogical reaction is in itself of interest for it leads directly to the deeper import of Doctor Petersen's studies. For this reaction *is* illogical; essentially it is no less reasonable to suggest that atmospheric changes may precipitate, for example, a thyroid crisis than to postulate that they cause a column of mercury to rise in a tube, or a recording lever to change its position. The difference lies only in conventionality of conception—in one instance a correlation has been universally accepted, in the other it should at least be held *sub-judice.*

The importance of Doctor Petersen's work lies in his attempt at a fundamental reorganization of medicine. Where theoreticians have but *stated* the need, he has *attacked* it in a practical way. He has, by way of a study in organismal adaptation, approached a tentative formulation of a methodologically practicable, synthetic, monistic theory of disease processes. Without any doubt in the reviewer's mind, intent and methodology vastly overshadow in importance results and conclusions. Before achievement comes trial, and Doctor Petersen has made a profound and arduous contribution.

His basic attitudes are derived from the Hippocratic *corpus*, in that he seeks a formulation of disease in terms that transcend the "pockets" of nosology and the vocabularies of artificially created, specialistic autonomous disciplines

(immunology, bacteriology, etc.). These he combines with a conviction that many biologists now share (see J. S. Haldane *The Philosophy of a Biologist*), namely, that physical and chemical data can be effectively applied to the study of disease only if one realizes and takes into account the fact that the essence of the phenomena of life is coördination and maintenance. But this homeostasis, Cuvier's "preservation of form in a stream of energy and matter," is in reality not a *status quo*, but a fluctuation within a narrow range in which are perceived cycles of biological rhythms. A study of these rhythms constitutes Doctor Petersen's point of attack. He has sought to establish that when patients are followed day by day clinically and chemically (and an exhaustive list of determinations were carried out, with emphasis on the vascular status and reactions, chemical and hormonal conditions, and the reactivity of the skin to inflammatory stimuli) there can be discerned a rhythmic change of state, oscillating between two antithetical poles. What these constellations are, the reviewer will leave to the reader to ascertain. A brief statement of them neither truly informs nor appears as reasonable as when buttressed by the text. The elements in terms of which these fluctuating states are described are familiar ones—oxidation, reduction, anabolism, catabolism, permeability, pH, etc.—elements which are involved in all physiological or pathological-physiological processes. All individuals exhibit these cycles, but there are quantitative differences ("the individual constitutional reactivity"). For example, in disease this biological flux may be unstable and excessive (as hyperthyroidism) or retarded and sluggish (as cretinism); and similar alterations accompany the widest variety of abnormal physical or psychical states. Many exogenous and endogenous factors condition this pendulation of the organism. But of these, Doctor Petersen's thesis states, and data are adduced to show, that meteorological changes play the most important rôle as stimuli, and do therefore condition the reaction of the patient or indeed initiate clinical alterations. A meteorological event to which the nicely attuned normal individual would react competently by highly labile, automatic mechanisms results in the actually or potentially inadequate patient in over-stimulation leading to functional exhaustion or over-response. For Doctor Petersen, therefore, the isolation of the individual is a fiction, and the organism is inseparably linked to the inorganic world about him. The human is thus in a very real sense a "cosmic resonator" and disease is but an expression of inadequacy to environment.

As regards tuberculosis, Doctor Petersen has in previous studies developed the significance of the focal reaction in the tuberculous individual. But he views this as not necessarily a specific immunological phenomenon, but he ascribes to the general metabolic status of the organism a far greater significance. Resistance becomes a physico-chemical-enzymatic phenomenon, and depends on whether the focus is digested or not. Digestion results in dissemination, and *vice versa*.

The potentialities of digestion of the focus will vary with the antipodal phases of metabolism (for example, increased permeability in one, and decreased in the other), the changing tide of dominance as between these being meteorologically conditioned. Hence the potential significance of the latter for the tuberculous. In this volume the discussion is limited to the presentation of data that in Doctor Petersen's opinion *demonstrate* that such is the case. Representative case histories are given in detail, and graphs are exhibited in which the ordinates are both meteorological and clinical data, and the abscissae are iso-temporals. Direct or inverse correlations are then pointed out between cyclonic events and disease phenomena. The conclusion is reached that meteorological changes influence the course of the disease both for good and evil, and play a rôle in the initiation or precipitation of clinical episodes in tuberculosis.

Thus Doctor Petersen's plan emerges in its entirety. These are an uncommon series of books; very few such projects have been carried through with such meticulous, arduous zeal, and masterly scholarship and scope. Yet this in no way implies freedom from error. Judgment of the "truth value" of this study, of the necessariness and sufficiency of its concepts must for the moment remain for individual judgment until, after digestion and analysis, group opinion crystallizes out. To read these books places no mean demands upon the reader. The text and commentaries are voluminous, but they contain a wealth of ordered medical information. The graphs are often bewilderingly complex; the reader will be continually plagued by questions as to the necessity or desirability of drawing causal connections between suggestively parallel or divergent curves; by the application of macro-climatological measurements to micro-climatological conditions. But perhaps, like the reviewer, he will come away from the book significantly stimulated by this literally heroic effort to give redirection to medical thought, to avoid the stalemate that seems to face current preoccupation with the working out of minutiae, and to introduce order and continuity into what, at the moment, is discrete and chaotic.

JOHN ALEXANDER: *The Collapse Therapy of Pulmonary Tuberculosis. With contributions of Chapters III and IV on Physiological Principles and Pathology of Pulmonary Collapse by* MAX PINNER; *Chapters XI and XII on Pneumothorax by* JOHN BLAIR BARNWELL; *Chapter XV on Oleothorax by* KIRBY SMITH HOWLETT, JR. *Pp. xiii + 705, with 367 illustrations and 6 plates, Charles C. Thomas, Springfield, Illinois, 1937, cloth, $15.00.*

*By* THOMAS J. KINSELLA

John Alexander's first volume, "The Surgical Treatment of Pulmonary Tuberculosis," published in 1925 at a time when collapse therapy for pulmonary

tuberculosis aside from pneumothorax was used to a very limited degree, brought to the medical profession of this country a very comprehensive review of this special field to the date of its publication. It soon became the accepted text on the subject and was undoubtedly responsible in many ways for the rapid development and popularization of this type of treatment.

The present volume has been greatly enlarged and completely revised in the light of the author's extensive experience and the marked changes and developments of the past twelve years. The opening chapter on the *Perspective of the Collapse Therapy of Pulmonary Tuberculosis* describes the material forming the basis of the author's studies, and contrasts the results obtained by sanatorium treatment of the disease with little or no collapse therapy, with those obtained by a combination of such treatment supplemented by the extensive use of surgical collapse. A review of the effects of collapse in minimal, moderately advanced, and far advanced tuberculosis and the possible field for its use throughout the United States follows. The discussion on the training of the thoracic surgeon and his relation to the sanatorium is particularly timely and pertinent.

The chapter on the *Evolution of Surgical Therapy*, revised and brought up to date since the original edition, briefly describes the development of the various surgical procedures and the men responsible for them and again presents photographs of the pioneers in the field of collapse therapy.

The *Physiological Principles of Collapse* and the *Pathology of Collapse* are admirably considered in two chapters by Max Pinner. Respiratory physiology under normal and pathological conditions is adequately discussed together with the alterations produced by the various types of collapse. The 45 pages devoted to this discussion are crammed full of interesting and valuable information gleaned from the writings of some 375 authors who are quoted. A thorough study of the material presented in these chapters is recommended to all who are interested in the treatment of pulmonary tuberculosis and other pulmonary diseases. An adequate application of much of this information in daily work may well distinguish the true thoracic surgeon from "just another rib cutter."

The chapter on *Choice of Operation* covers a very difficult subject in an excellent manner. The advantages and disadvantages, indications and contraindications of the various types of collapse are discussed fully and impartially. A careful study of the 84 diagrams and the descriptive material accompanying them, illustrating numerous complicated problems in the choice of the proper procedure or sequence of procedures, will prove of great value to all interested in the subject, as they depict more clearly than many pages of descriptive material the attitude of the author and his coworkers toward the handling of tuberculous pulmonary disease.

Three chapters, a total of 63 pages, are devoted to surgery of the phrenic

nerve. Full consideration is given to the anatomy and physiology of the nerve, the technique of surgical approach, and to the direct and indirect effects of interruption, as well as to the results obtained by the use of the procedure. The author gives a fair and impartial consideration to this controversial subject, concluding that the procedure is of definite value where indicated, but stressing the importance of temporary over permanent interruption.

Chapters XI and XII by John B. Barnwell are devoted to a discussion of unilateral and bilateral pneumothorax. The subject is handled in an excellent manner and the text is supplemented by numerous abstracts of case histories and reproductions of roentgen films. A wealth of valuable material for the guidance of the clinician is included. A chapter on closed and another on open *Intrapleural Pneumonolysis* follow. A separate chapter on *Oleothorax* by Kirby S. Howlett, Jr. carefully discusses the technique, indications, contraindications and results of the therapeutic use of oil in the pleural cavity. Extrapelural pneumonolysis with the various types of filling material is adequately described in two chapters. Short chapters are also included on *Bilateral Collapse Therapy*, *Scaleniectomy*, *Intercostal Neurectomy*, *Surgical Drainage of Pulmonary Cavity*, *Tuberculous Empyema*, and *Tuberculosis of the Chest Wall*.

Extrapleural thoracoplasty is extensively considered in nine chapters, devoted to indications and contraindications, preoperative management, anaesthesia, technique, development of the modern operation, anterior operations, reoperations, postoperative management, and the changes brought about by thoracoplasty and to an extensive discussion of results. The numerous changes which have occurred in the technique and application of this procedure since the publication of the first volume are thoroughly discussed. The consideration of preoperative and postoperative management are particularly valuable, for the success of the operation on many a patient is determined by proper handling before and after surgery. This section is by far the most complete and valuable dissertation on the subject which has been produced to date.

Throughout the entire volume, the text is presented in a clear, concise manner which makes it easy to read and follow. The authors have presented their subjects impartially, exhibiting the balanced judgment obtained by careful analysis of all information at hand with no suggestion of the crusading spirit. Their descriptions of technique are simple yet adequate. The diagrams and photographs, which are used freely, are clear and sharp and are accompanied by terse descriptive material. Case histories are used freely but are short and contain no unnecessary material. All sections of the book are profusely illustrated by reproductions of X-ray films which are clear and sharp with special markings added to emphasize the important details shown. The composition and printing are excellent. The use of numerous subheadings

throughout renders the finding of special material an easy task, and makes the work more valuable as a reference volume. The book is carefully indexed for ready reference. An extensive bibliography of 1,342 titles is included for the convenience of the reader who wishes to refer to the original articles.

Without a doubt, this masterpiece of Doctor Alexander's is by far the best volume which has appeared on this subject to date and contains a wealth of descriptive and reference material. A copy of it should be in the hands of everyone who is interested in the modern treatment of pulmonary tuberculosis.

POL N. CORYLLOS: *The Surgery of Pulmonary Tuberculosis. Pathologic Physiology, Indications, Procedures, Complications and Results. Pp. ii + 152, with 69 illustrations and 28 tables, Brooklyn, New York, Comet Press, Inc., 1937, paper, $2.00.*

By RICHMOND DOUGLASS

This group of essays deals with the application of collapse therapy in its surgical forms to the treatment of pulmonary tuberculosis. The magnitude of the problem is appreciated when it is realized that approximately 700,000 men, women and children are ill with tuberculosis in the United States. The monograph is limited to the clinical and laboratory experience of the author. Emphasis has been given to the physiology and mechanics of the tuberculous lung. The value of pneumothorax as a collapse procedure is conceded, but an earnest plea is made that unsuccessful pneumothorax should not be unduly prolonged to the exclusion of surgery in the form of thoracoplasty which may be the more efficient though more dangerous method.

The author's views regarding pathological physiology, anatomy and respiratory mechanics of the lung, and of bronchial obstruction are briefly stated. The tuberculous lung and the process of cavity formation are discussed with emphasis on the importance of obstruction of the bronchial outlet as a requisite to cavity healing. No explanation is offered, however, as to the fate of retained secretions, nor is any citation made of postmortem confirmation of this mode of cavity healing.

Recognition is given to the significance of indications in determining surgical treatment and the discussion dwells particularly upon the type of tuberculous disease present. Acute cases fall into two groups, the exudative benign form, and the caseous pneumonic form which "can be differentiated by marked etiological, microscopical, clinical, and therapeutic characteristics . . . but the real pathognomonic signs are revealed by serial and repeated X-ray examinations which show the appearance of cavities." No safe and certain diagnosis

can be made until resolution in the first or cavitation in the second has taken place. Surgical treatment should be deferred and utilized only after the cavities have shelled out. The chronic caseous pneumonic lesions represent the "surgical cases" while patients with the chronic productive form of tuberculosis do not require collapse for they "are not dangerous either to themselves or to the community."

Surgery in tuberculosis is synonymous with the treatment of cavities. Pneumothorax is usually the first mode of attack, but may be defeated by the presence of adhesions which in the author's opinion prevent cavity closure because they maintain the patency of the draining bronchi. However, the successful severing of adhesions does result in cavity closure, and therefore establishes pneumonolysis as an important adjunct to pneumothorax.

The chapter on surgical technique describes the equipment devised by the author for pneumonolysis and pictures his thoracoplasty instruments. The technique utilized in these operations is fully described. Extrapleural apicolysis with plombe is also discussed, as are phrenic nerve operations and the treatment of tuberculous empyema. The necessity of crushing the phrenic nerve "for a distance of 1 cm." as a means of producing temporary paralysis is open to question.

The complications associated with the surgical procedures are discussed, with emphasis on pneumothorax and on thoracoplasty. The sections dealing with atelectasis, paradoxical respiration, postoperative pneumonias and spreads, and shock are instructive. The importance of the postoperative aspirations of excessive bronchial secretions is rightly stressed.

A series of 21 tables presents the results of the surgical treatment of 968 patients during the period July, 1931 to June, 1936. The surgical procedures are separately considered, with especial emphasis on thoracoplasties which are considered according to age, sex and race. In all tables the results are expressed in terms of mortality or of sputum status. In no place is reference made to the functional capacity of the patients credited with a negative sputum. The statistics referring to phrenic nerve operations are confusing; one hundred operations were performed on patients with a preëxisting pneumothorax, while in 24 a phrenic operation was the only procedure used, yet judgment was passed on this measure on the basis of a total of 142 cases. Scaleniotomy showed limited efficiency in a group of 28 cases. Apicolysis with plombe was performed in 21 cases in 1931–1932, and was then abandoned. Pneumonolysis was credited with securing 70 per cent of negative sputum in a group of 93 unilateral cases. No credit is given to the basic pneumothorax nor is any reference made to the ultimate hazards of pneumothorax which were quite possibly increased by the effusions complicating pneumonolysis. Effusions developed in 62 per cent of the total group of 250 cases, and although

tuberculous empyema resulted in only 2.5 per cent, they doubtlessly resulted in pleural thickening in others. The results of thoracoplasty in a group of 529 patients are presented. Death occurred in 34 of 343 unilateral cases, in 31 of 108 bilateral cases and in 32 of a group of 78 patients who had tuberculous empyema with mixed infection, extensive revisions of thoracoplasties, or Schede operations, making a total of 97 deaths. Two hundred and fifty patients were discharged with negative sputum, while the remainder, 182, had either left against advice or were still in the institution.

There is evidence of hasty preparation of the material; but the volume as a whole is stimulating to thought and well worth perusal.

The monograph is printed on good paper and is well illustrated.

RAYMOND SWYNGHEDAUW: *Le moignon pulmonaire dans le pneumothorax thérapeutique. Pp. v + 113, with 56 illustrations, Gaston Doin & Cie, Paris, 1937, paper, 30 fr.*

By MAX PINNER

The present studies were undertaken in an attempt to elucidate further some of the physiological principles governing hypotensive pneumothorax. The methods of approach were roentgenological observation, radiokymography and, in regard to certain details, experimental studies. The main conclusions are: (*1*) that the pulmonary lobes, unless the interlobar fissures are obliterated, are mechanically independent units and, in hypotensive pneumothorax, are frequently "dislocated" from their normal relation; (*2*) that the lobes in normal conditions have an individually differing retractability, the upper lobes retracting more than the lower ones under equal intrapleural pressure; (*3*) that the respiratory motion of the upper lobes is caused by the motion of the upper ribs and that of the lower lobes by that of the lower ribs and of the diaphragm; (*4*) that under certain conditions phenomena arise which the author summarizes as *la grande expansibilité des lobes sains*; (*5*) that atropine, in the majority of cases, increases intrapleural pressure, presumably by causing a reaeration of perifocal atelectatic areas.

All these findings, essentially an elaboration and refinement of previous work, are used to create a more complete picture of the physiological changes in and the therapeutic potentialities of hypotensive pneumothorax. The different elastic properties of the individual lobes are, in the author's opinion, more potent factors in the genesis of selective collapse than the weight of the lung, a factor that is greatly stressed by Parodi in Italy and by Dumarest in France. In regard to these discussions one can hardly suppress the suggestion

that medical arguments on matters of physics might better use physical terms according to their accurate definition. In this study, as in many others on this subject, the popular notion, as against the scientific definition, is carried over that elasticity is that property that makes it so easy to stretch a rubber band.

The most original part of this monograph presents radiokymographic studies on pneumothorax cases. These elaborate observations have not produced any original facts, though they have confirmed and put on a more quantitative basis the notions that Sergent in particular has propounded for some time about the independence of the pulmonary lobes. However, it would hardly be fair to judge by this particular work the significance of radiokymographic studies in respiration. On the other hand, we find at least one example for the danger of overreliance on one single method of examination: the kymographic tracings show that the inspiratory expansions of the upper lobes are parallel to but greater than the inspiratory movements of the upper ribs. Hence the conclusion that the upper lobes are motivated exclusively by the movements of the upper ribs. Without the aid of such tracings it is obvious that the inspiratory descent of the diaphragm cannot be without influence on the degree of expansion of the upper lobes; and it is precisely this influence that explains the recorded but undiscussed fact that the upper lobes expand more than their alleged sole motivators, the upper ribs.

The individually different elasticity of the lobes, established for dog's lungs, should be confirmed for human lungs.

The syndrome of the "great expansion of the normal lobes," the physically necessary counterpart of selective collapse under sufficiently low intrapleural pressure, is presented as a somewhat mysterious phenomenon. It is better known as the compensatory emphysema of the uninvolved lobes.

The pharmaco-dynamic influences that may be exerted upon intrapleural pressure by way of the vegetative nerve system need much further work. It would seem desirable not only to study a wider range of pharmaca, but to analyze through which particular action such influences are mediated. There is the possibility that such drugs alter the midposition of the thorax, the relative distribution of the circulating blood, the secretory function or the width of the bronchi; they may affect the permeability of pleural and capillary surfaces, and so on. Doctor Swynghedauw does not venture an opinion on these questions.

In a summarizing advice to the reader it should be said that this monograph contains a good deal of importance to those interested in the basic and theoretical principles of pneumothorax, but little for those concerned only with its practical application.

SAMUEL A. LEVINSON AND ROBERT P. MACFATE: *Clinical Laboratory Diagnosis. Pp. 877, with 144 engravings and 13 plates, Philadelphia, Lea & Febiger, 1937, cloth, $9.50.*

*By* MAX PINNER

There is a considerable number of books on clinical laboratory diagnosis on the market. A new book on this subject must justify its appearance. The authors of this book have followed a definite aim in a definite way. They wished to provide "to the student, interne, practising physician and technician a suitable review of clinical laboratory diagnosis sufficient to meet their general needs" and they wished, in regard to each procedure, to anticipate a minimum of actual knowledge on the part of their readers. These aims are achieved by brief and basic clinical and pathological statements in addition to the principal information, namely technical procedures. These statements are not meant as primary information, but rather as aids to a failing memory, or as recrystallizations of previously available knowledge. These statements are as authoritative as their concise oversimplification will permit. Essentially the same is true for the enumeration of the clinical conditions in which a given laboratory result may be obtained.

The authors have paid particular attention to the practicability of their text in actual work. This leads to a unique plan of an elaborate but simple system of cross-references within the text, obviating many a search in the index of the book. This arrangement has the further advantage of avoiding repetition without a loss of clarity and completeness. Anyone who has used this book as a constant companion in laboratory work for some time will readily realize the great aid that this particular arrangement provides.

While the tenor of this work is a sound conservatism, and while it is a thorough and reliable guide, it might be suggested for later editions that are bound to appear, that a sharper distinction be made between fundamentally important procedures and auxiliary tests of questionable usefulness.

The many illustrations are well chosen and adequately reproduced.

As a whole, it seems to this reviewer that this text is a valuable addition to the existing books in this field because it is accurate in information, lucid and concise in style, and infinitely more practical and time-saving at the work bench than most other similar works. Any laboratory worker in tuberculosis hospitals, physician or technician, should be well equipped with this book and one of the well known more specific texts, such as the one by Willis or by Baldwin, Petroff and Gardner.

NATHAN RAW: *The Control of Bovine Tuberculosis in Man. Pp. viii + 128, with 12 illustrations, London, Bailliere, Tindall & Cox, 1937, cloth, 6s.*

By HENRY STUART WILLIS

The burden of this little book is a worthy and important one, especially to the British for whom it was written primarily. It points out the dangers to human beings from the intake of milk which comes from the tuberculous cow. It emphasizes over and over again the facts that (*1*) the incidence of tuberculosis in cattle is high in the British Isles; (*2*) about ten per cent of the milk sold for human food is contaminated with bovine tubercle bacilli; (*3*) 2,000 children in England and Wales die annually from tuberculosis of bovine origin and 4,000 develop the affection in varying forms; (*4*) prophylactic inoculation of a living, nonvirulent strain of human tubercle bacilli protects calves from the inroads of the disease.

The author's evaluation of the needs in the present circumstances takes into account several issues. The expense involved in the plan of eradication by slaughter of all reacting cattle is deemed too great and is not advised. But the Bang method of separating calves from mothers at birth and the compulsory pasteurization of milk are defended and vigorously advocated.

The book warns of the dangers in the situation, yet it contains much matter which is needlessly uncorrelated. Its 12 chapters have distinct titles, but the subject matter of one may be repeated one or several times in several other chapters. One gains the net impression that these chapters had been used as separate essays or addresses and had later been brought together into book form without very much correlation.

This work contains much that is vague and indefinite, especially where results from vaccination of calves are concerned. The data used in several of the tables are old—some of them dating back to the earlier work of the British Royal Commission. This causes the reader to wonder concerning the present-day status. The story is given of therapeutic vaccine—a kind of tuberculin prepared from dried, pulverized, avirulent tubercle bacilli of which the bovine bacillus goes into the preparation used for the treatment of calves. Twelve well executed illustrations embellish the book and, to some extent, supplement the subject matter dealt with in adjacent pages. Mortality experience is referred to rather loosely. On page 26 it is stated that 3,000 children under the age of 10 die annually of bovine tuberculosis in Great Britain: on page 44, 2,000 die in England and Wales, and on page 62, 10,000 die in the British Isles each year. The author makes several sallies into the field of theory when he attempts to support his idea of mutation of tubercle bacilli from bovine to human type by depending upon ratiocination and citation of unproved case reports.

Taken altogether the book should do good in still further directing attention to what appears to be a deplorable condition.

I. J. PARDO: *Base para la interpretación de la radiografía del tóraxd el adulto. La imagen en el sujeto sano (proyeccion dorso-ventral). Pp. 114, with 67 figures in the text, Lit. y Tip. del Comercio, Coracas, 1937, paper.*

*By* I. BIRD-ACOSTA

Basing his work on the study of routine radiographs of the chests of healthy university students (cases with a history of contact with tuberculosis or of pulmonary disease were carefully excluded) I. J. Pardo presents an interesting and useful monograph on normal shadows which are apt to prove confusing in the interpretation of radiographs of the chest.

The author divides the radiographic shadows of the normal chest into the following groups: (*1*) soft tissues; (*2*) bony framework; (*3*) diaphragm; (*4*) midthoracic shadow; (*5*) pulmonary parenchyma; (*6*) pleura; and (*7*) areas of calcification.

By the aid of good reproductions and diagrams attention is called to the unusual shadows which may be produced by the soft tissues. These include the shadow of the sternocleidomastoid muscle which may simulate infiltration or cavitation at one or both apices, especially when it gives rise to the so called hour-glass shadow; the *pectoralis major*, and the breast, including the nipple, whose shadow may at times be mistaken for an area of nodular infiltration; and lastly cutaneous folds, particularly over the clavicle, which in thin subjects give rise to a narrow band several millimetres in thickness which runs alongside the superior border of the clavicle.

In discussing the bony framework of the thorax, the author points out that in many cases the natural curvature of the ribs places the costal groove in such a relationship to the beam of the X-rays as to produce lineal effects in the inferior arch which may be puzzling. These effects have been previously described by Alban Kohler. Not infrequently the borders of the costal grooves appear unusually prominent and manifest themselves in the radiograph by thin crest-like projections in the lower border of the ribs. An anomalous ossification of the costal tubercle is another finding which is apt to lead to erroneous conclusions. This is generally observed in the upper ribs and is usually bilateral.

A thin exostosis arising from the margin of a rib may simulate a parenchymatous infiltration.

When studying the diaphragmatic outline one should not confuse the so called double or multiple-dome diaphragm with pleural adhesions. This

phenomenon is attributed to irregular contraction of the muscle bundles of the diaphragm, which break up the normal diaphragmatic curve into two or more segments.

Obliteration of the cardiophrenic angle may be produced by a cardiodiaphragmatic ligament, the inferior vena cava, and, on occasions, by the transverse process of a vertebra.

The components of the midthoracic shadow are reviewed and attention is called to an almond-shaped shadow which is frequently observed at the inner extreme of the sixth right posterior interspace (the so called nodule of Ottonello) which is interpreted by various authors as being produced by the azygos vein.

Ordinarily, healthy pleura is considered radiotranslucent, but the author believes that in many cases where the interlobar pleura is visualized as a very fine and perfectly regular line the phenomenon may not have any pathological significance and, as proof of this, he cites cases of his own and other investigators where the tuberculin test was consistently negative and, at necropsy, no evidence of a thickened pleura was noted. The azygos lobe may be considered as another example of visualization of perfectly normal pleura.

Although pulmonary calcifications are not, strictly speaking, normal shadows the author includes them in his discussion inasmuch as 20 per cent of his healthy subjects presented such evidence.

The facts in this monograph are clearly presented and the illustrations well chosen.

The book was intended primarily for the use of medical students and general practitioners who might find it necessary to interpret their own radiographs, but the roentgenologist and phthisiologist will also find much valuable and interesting information within its pages.

J. FRIMANN-DAHL AND GEORG WAALER: *Röntgenologische und pathologisch-anatomische Studien über den tuberkulösen Primärkomplex. Acta Radiologica Supplementum xxxiii. Pp. 60, with 24 illustrations, Nationaltrykkeriet, Oslo, 1936, paper.*

By MAX PINNER

These studies were prompted by the peculiar epidemiological situation of tuberculosis in Norway where the total frequency of tuberculin reactors is considerably lower than in most other European countries and where a relatively large proportion of primary infections take place in late adolescence and in adult life. According to pathological data available and to tuberculin surveys it appears that primary infections have shifted toward older age groups during the last two decades.

The authors examined with roentgenological and pathological methods 200 consecutive necropsies; in 142 of these, they were able to identify a primary complex. The detailed studies reaffirmed the pathognomonic character of the primary complex, as elaborated by an illustrious sequence of pathologists. In several adults, a fatal tuberculosis was found in the presence of an obviously recent primary complex. These cases are pointed out in support of the opinion that primary infection in the adult leads not infrequently to progressive disease without the intervention of a latent phase. The number of such cases is so small that no valid conclusions seem justified as to the actual frequency of such occurrences; they are sufficient, however, to prove the actuality of such developments. Considerable scepticism is permissible in regard to the estimation of the age of tuberculous lesions, and of primary complexes in particular, on the basis of exclusive morphological observation. Absence of calcification, the main criterion for the relative youth of primary foci, is not a reliable index, as has been stated repeatedly. This reviewer has observed noncalcified primary complexes that were several years old, and one such case in which bacteriological evidence of tuberculosis extended over seven years preceding death.

The authors studied thoroughly all the nontuberculous lesions that produced roentgenological shadows of calcium density; they found calcified thrombi or emboli in six cases, small, coral-like intraälveolar ossifications in seven cases, anthracotic and silicotic nodules (number of cases not stated), calcifications and ossifications in thickened pleura in 48 cases. In a person, dead by drowning, several small pebbles were found, and in two cases bits of wood and cellulose with calcific incrustation in subpleural position.

The frequency and multiplicity of nontuberculous foci of calcium density should warn against the ready diagnosis of tuberculosis whenever calcified foci are demonstrated by X-ray.

This little monograph is well illustrated; it shows the careful study of the pertinent material and the conservative interpretation, that are an established tradition in Professor Harbitz's Institute.

The Medical Committee of Air Hygiene Foundation of America, Inc., Medical Series, Bulletin No. 1. *Silicosis and Allied Disorders, History and Importance. Pp. 178, with 17 figures in the text, Pittsburgh, Mayer Publishing and Printing Company, 1937, paper.*

By JOHN E. CULP

This volume opens with an introductory chapter defining pneumonoconiosis, silicosis, and asbestosis. The protective mechanisms of the human respiratory system are discussed in relation to inorganic dusts present in a constantly

increasing number of industrial processes. The pathogenic importance of dust-particle size is stressed. An attempt is made to classify dusts with respect to their ability to produce disease in humans; the book is limited in its discussion to inorganic dusts, nontoxic in the usual sense.

More than half of the bulletin is devoted to a history of silicosis both in foreign countries and the United States, enumerating, by occupation and industry, dust hazards, present and potential. Experimental and industrial research is delineated to show where dust hazard exists. In addition the fact is pointed out again that not all cases of pneumonoconiosis are characterized by increased susceptibility to tuberculosis. Experimental research in the United States is considered, covering many varieties of dusts and their particular effect on lung tissues with and without added infection.

A clear and concise statement concerning what is known about silicosis comprises the concluding chapter. In this section, good photographic reproductions of gross and microscopical sections add value to the text. The diagnostic approach to the problem includes the well known methods and stresses rightly the roentgenological examination. An outline of proper roentgenological technique is submitted. Well conceived summaries comparing roentgenological and histological appearances in healthy lungs, in simple silicosis and in silicosis with infection are presented.

The bulletin is well written and contains much excellent material for the physician or layman interested in industrial hazards. Particular attention is given to the chapter dealing with "what is known about pneumonoconiosis—especially silicosis, what is controversial, and in what particular directions research should be supported by the Foundation. . . ." A comprehensive review of the literature is contained in an exhaustive bibliography.

The foreword states: "Chapters I, II and III were prepared for the Medical Committee by Eleanor Rantoul, Research Assistant, Industrial Health Section, Metropolitan Life Insurance Company, New York. The members of the Committee edited these chapters and prepared copy for chapter IV, which Miss Rantoul then put in order for printing."

H. B. Meller is the Managing Director, and the members of the Medical Committee are: Drs. A. J. Lanza, L. U. Gardner, S. R. Haythorn, T. L. Hazlett, R. R. Jones, E. P. Pendergrass, O. A. Sander and R. R. Sayers.

LETTERIO CANNAVÓ: *La broncospirochetosi di Castellani. Pp. 102, with 20 illustrations, L. Salpiertra, Editore, Palermo, 1937, paper, Lit. 18.*

By GEORGE W. WEBER

Ever since Castellani described it in 1905, bronchial spirochetosis has been recognized as a distinct clinical entity. Its aetiological agent, the bronchial

spirochete, (the specific identity of which, however, has been disputed by many) is polymorphous, variable in length, presenting pointed extremities and no flagellae. In stained preparations it shows coccoid bodies. These are thought to be a reproductive phase of the spirochete and are considered its main differential characteristic. Cultures and animal inoculations have as a rule given unsatisfactory results.

No specific biological reactions are produced in the individuals affected and the Wassermann reaction is negative, unless syphilis is also present. The pathological changes reported in necropsies are few. Patches of consolidations in the lungs and bronchiectatic dilatations may be present. In one case (Dagini and Strozzi) the bronchial walls presented angiomatous vascular neoformations, which are thought to be responsible for the frequent haemorrages, one of the characteristic symptoms of the disease.

Other symptoms are slight elevation of temperature, tracheobronchitis with cough and mucopurulent sputum which is occasionally fetid, and which on standing will settle in two layers. A few bronchial râles may be the only physical signs elicited, and the X-ray picture will more often than not reveal only an increase of pulmonary markings and some peribronchial fibrosis. Mitral stenosis, syphilis of the lungs, pulmonary mycoses, etc., and especially pulmonary tuberculosis have to be considered in the differential diagnosis. Ultimately the positive diagnosis will have to stand on the presence of the spirochete in the sputum. The disease is highly contagious, especially in the acute stage, and two epidemics of it were spread in France by colored troups in 1917 and in 1924.

The treatment is based principally on prolonged and repeated administration of arsphenamine, and the results depend on the tempestivity of its application. Boccia has suggested, and some Argentinians have tried successfully, inhalations of chloroform, a single treatment being sometimes sufficient.

Although he adds nothing new to our present knowledge of bronchial spirochetosis, Cannavó has given us an excellent and comprehensive study of the disease. It has been his good fortune to observe and to treat nineteen cases in different stages of the disease during a relatively short period and he reports in detail their clinical histories and the fruits of his observations.

The monograph is illustrated with several good reproductions of photomicrographs and radiographs, and it contains a list of 141 references. It also contains a geographical, as well as chronological index of the more important publications on the subject.

ROQUE A. IZZO AND OTHERS: *Anales del Centro de Investigaciones Tisiologicas. Pp. 526, with illustrations accompanying the separate articles, Buenos Aires, Argentine, La Imprenta Mercatalia, 1936, paper.*

By ESMOND R. LONG

The collection of studies included in this volume covers a wide range in the field of tuberculosis investigation. Various members of the staff of the *Centro de Investigaciones Tisiologicas* have collaborated in its production. The several branches of this institution comprise medical and surgical clinics, a prophylactic social service department, a division of roentgenology, laboratories and a library and statistical department. The scope of the library is indicated in a series of appendices to the volume.

The assemblage opens with a careful study of the pathological anatomy of the collapsed lung following thoracoplasty. In the healing fibrotic process stress is laid upon the pleuroparietal irritative reaction. In an epidemiological study aimed to determine the source of disease in one hundred tuberculous women, direct contagion could not be established in about 40 per cent. Low economic status appeared an important factor, while data for occupation proved inadequate for determining the rôle of this factor. A number of the twenty articles included in the collection are concerned with chemical investigation in the field of clinical tuberculosis, particularly with the effect of tuberculosis on renal function. Interesting cases are recorded, but, unfortunately, it is not clear how much of the renal damage reported may have been due to the gold therapy employed. The relation of tuberculosis and cancer of the lung is brought up, and although metaplastic proliferation of new epithelium in tuberculous cavities is described, the total independence of the cancerous growth in other cases is stressed. A number of interesting case reports of complications of tuberculosis are presented.

The book is to be commended as an expression of active investigation in a centre concerning itself with all phases of tuberculosis. It can be of interest everywhere, as summaries of the articles are given in English, French and German as well as in Spanish. The summaries in the foreign tongues would be improved by submission to one for whom the language is native, although they are readily understandable. Later editions should improve the quality of the illustrations, particularly the photomicrographs.

*Health in Colleges. Proceedings of the Second National Conference on College Hygiene, pp. 112, New York, National Tuberculosis Association, 1937, cloth.*

By HENRY STUART WILLIS

This little book records the deliberations of the second National Conference on College Hygiene, which is sponsored by the President's Committee of Fifty

on College Hygiene, the National Health Council and the American Student Health Association.

This body has passed beyond the concept of student health as it concerns mere absence of illness, and has embraced the idea that "physical, mental and emotional hygiene," and to some extent personal and social behavior, fall within the province of college hygiene. It calls upon college administrators and officials to recognize new and larger responsibilities and objectives in maintaining student health on conventional lines of prevention and care of actual disease; in providing an environment that is conducive to the best in physical, mental and social hygiene; in furnishing college students with health instruction that encompasses these broad concepts; in bringing before the student special information, in particular problems of hygiene that are more or less peculiar to student life, and in teaching such students as elect the work the basic principles of school hygiene in this broad sense, so that they may themselves become teachers in the field.

The book is compact and well bound. It should serve as a base-line guide in administration of such work.

*Manual of Tuberculosis for Public Health Nurses. New York State Department of Health, Division of Public Health Nursing and Division of Tuberculosis, Albany, New York, pp. 65, paper.*

By RUTH W. HUBBARD

Although originally prepared for the use of public health nurses in New York State by the Divisions of Public Health Nursing and Tuberculosis, this manual will be welcomed by public health nurses everywhere. Since we recognize that tuberculosis is both a family and a community problem, it is apparent that the nursing responsibility for these patients cannot rest entirely with any one group of nurses. The author presents a manual which emphasizes at once the wide variety of community relationships necessary to an effective tuberculosis program. Thus all public health nurses meet the tuberculous patient at some point in their work, and feel a need of equipment to which the handbook in question supplies a most stimulating response. To the nurse whose major interest lies in the field of tuberculosis, it will bring that valuable assistance which establishes new goals in answering questions.

Since any effective worker brings to her field thorough knowledge of her subject, the nurse in tuberculosis must know the disease. Therefore a description of tuberculosis itself opens the manual. With admirable wisdom the discussion of community relationships follows immediately, since it is important for the worker to appreciate promptly her position as one of a group in the program of control.

By its title a manual commits itself to the task of "telling how." Frequently such instruction is confined to a description of how certain technical procedures can be most effectively carried out. Here the discussion includes sound suggestions concerning the successful establishment of helpful relationships with the patient and his family. The patient and his needs, with the procedures for community protection, form the basis of all program developments. This is handled with insight in the chapters on nursing procedures and clinics. The chapter on records discusses not only the type of information needed, but also the equally important matters of good judgment in using the material secured and of skill in obtaining the desired data. The case for good records is made more impressive by a straightforward discussion of the use of judgment in determining visiting schedules and case loads only possible when adequate records are kept. The nursing procedures involved at each point of the patient's career are covered carefully. Finally, the manual presents a practical measuring rod for the nurse herself by suggesting periodic appraisal of the nursing service as a means of determining progress.

The understanding handling of the patient as the centre of the program, the sound suggestions as to method, and the guides to the development of good judgment in the nurse's planning make this handbook a welcome and valuable addition to our reference material.

*Brief Comment*

ANTONIA CARLET: *Histoire des idées sur la guérison des cavernes depuis Laennec. Pp. 74, Paris, Amedée Legrand, 1937, paper.*

Recalling that Laennec had fairly clear conceptions of the possibility and mechanism of healing of pulmonary tuberculous cavities, the author traces the varying ideas on the question since then. It is, therefore, a review of and comment upon the literature. Carlet finds the theory inviting and logical that obliteration of the draining bronchus is an important mechanism in the healing process.

A. BACMEISTER: *Die klimatische Behandlung der Tuberkulose und ihre heutige Bewertung. Pp. iii + 28, Berlin, Julius Springer, 1937, paper, RM 1.80.*

This brief pamphlet is a general and fairly vague discussion of the rôle of climatotherapy with rather more than the usual *pro-domo* tendency in such arguments. This is felt all the more because it is presented without documentation and without report of results. Excerpts: "the use of one definite climatic location in all forms of tuberculosis must lead to failure." "The best results in the cure of all forms of tuberculosis have been achieved in the

spas of higher altitudes without much wind." "Therefore the mountains of moderate altitude (Mittelgebirge) present to begin with the universal indication for pulmonary tuberculosis."

Professor Bacmeister's sanatorium is located in such a *Mittelgebirge*, the Black Forests; he should have authoritative experience in this matter.

*Books Received*

ECOT, F. CH., AND JULLIEN, W.: La thoracoplastie par voie axillaire. Preface by Dr. E. Rist. Pp. 47, with 31 illustrations, Gaston, Doin & Cie, Paris, 1937, paper, 18 fr.

KANTOR, JOHN L.: Synopsis of Digestive Diseases. Pp. 302, with 40 illustrations, C. V. Mosby Company, St. Louis, Missouri, 1937, fabrikoid.

LEMOINE, J.-M.: La thrombose de l'artère bronchique cause de dilatation bronchique chronique de l'adulte. Pp. 189, with 27 illustrations, Paris, Librairie E. Le François, 1936, paper.

# PRESENT TREND OF CASE FATALITY RATES IN TUBERCULOSIS[1]

GODIAS J. DROLET[2]

Recently Frost (1) suggested very thoughtfully that "a careful review of the history of almost any infectious disease will show that in each generation, even in each decade, as knowledge and understanding have grown, ideas as to the efficacy of control measures have had to be readjusted. In each period measures of control which seemed appropriate have been either overestimated or underestimated;" that we could "come to a better balanced view . . . only if we keep open minds" and inquired "whether our measures are well adapted to expectations."

There is probably no one infection against which so continuous and so wide an effort is being made toward control as tuberculosis. In the United States, at the present time, for institutional or sanatorium care alone there is now being spent more than $100,000,000 annually. In certain communities tuberculosis patients in public institutions occupy nearly one-fifth of all hospital beds. Particularly in the United States and in Great Britain there has been extensive, systematic provision for the care of such patients. It may, therefore, be useful to weigh the success or failure in attaining the main objectives, which of course are, first, assuring as far as possible the recovery of the patients and, second, more important to the community, control of the spread of infection. With declining cases and deaths a common observation, there can be little question but that, between improved conditions of life and increasing provision for the sick, some control of the infection is obviously being achieved. On the other hand, is definite progress being made in the treatment of the disease now that there is available in many places a number of hospital beds sufficient to receive most of the active cases who seek public care and, of late, new and radical forms of surgical treatment are being used in an increasingly greater proportion of the patients?

[1] From addresses presented before the American Epidemiological Society, New York City, April 23, 1937, and the Eastern Section of the American Sanatorium Association, Scotch Plains, New Jersey, November 12, 1937.

[2] New York Tuberculosis and Health Association.

What effect, if any, have these facilities and measures had upon case fatality rates in tuberculosis?

The data presented here and the discussion are directed solely at the question of what results are being obtained or reflected upon the com-

TABLE 1

*Tuberculosis, New York City, Chicago—ratio of deaths to reported new cases*

| YEAR OR PERIOD | NEW YORK CITY* (PULMONARY) | | CHICAGO† (ALL FORMS) | | YEAR OR PERIOD |
|---|---|---|---|---|---|
| | Cases‡ | Deaths | Cases‡ | Deaths | |
| 1915 | 22,141 | 8,825 = 40% | 12,709 | 4,204 = 33% | 1915 |
| 1916 | 19,297 | 8,411 = 44% | 12,017 | 3,734 = 31% | 1916 |
| 1917 | 17,494 | 8,825 = 50% | 14,908 | 3,800 = 25% | 1917 |
| 1918 | 14,439 | 8,779 = 61% | 16,567 | 3,827 = 23% | 1918 |
| 1919 | 14,570 | 7,395 = 51% | 15,607 | 3,244 = 21% | 1919 |
| 1920 | 14,035 | 6,165 = 44% | 10,747 | 2,652 = 25% | 1920 |
| 1921 | 12,966 | 5,143 = 40% | 10,593 | 2,325 = 22% | 1921 |
| 1922 | 13,329 | 5,033 = 38% | 10,519 | 2,220 = 21% | 1922 |
| 1923 | 11,336 | 4,951 = 44% | 10,105 | 2,335 = 23% | 1923 |
| 1924 | 11,934 | 4,780 = 40% | 8,634 | 2,434 = 28% | 1924 |
| 1925 | 10,955 | 4,776 = 44% | 7,709 | 2,489 = 32% | 1925 |
| 1926 | 10,498 | 4,828 = 46% | 8,504 | 2,530 = 30% | 1926 |
| 1927 | 10,873 | 4,444 = 41% | 7,798 | 2,567 = 33% | 1927 |
| 1928 | 11,614 | 4,636 = 40% | 7,085 | 2,680 = 38% | 1928 |
| 1929 | 11,938 | 4,507 = 38% | 6,540 | 2,548 = 39% | 1929 |
| 1930 | 11,821 | 4,457 = 38% | 6,118 | 2,235 = 37% | 1930 |
| 1931 | 11,794 | 4,370 = 37% | 6,219 | 2,290 = 37% | 1931 |
| 1932 | 10,589 | 3,997 = 38% | 5,865 | 2,027 = 35% | 1932 |
| 1933 | 9,991 | 4,056 = 41% | 5,485 | 2,038 = 37% | 1933 |
| 1934 | 9,990 | 3,950 = 40% | 5,581 | 1,940 = 35% | 1934 |
| 1935 | 8,796 | 3,968 = 45% | 5,834 | 1,946 = 33% | 1935 |
| 1915–17 | 58,932 | 26,061 = 44% | 39,634 | 11,738 = 30% | 1915–17 |
| 1933–35 | 28,777 | 11,974 = 42% | 16,900 | 5,924 = 35% | 1933–35 |

* From reports of the Department of Health, City of New York.

† From reports by courtesy of the Chicago Municipal Sanitarium.

‡ Including those identified from death certificates.

munity reports by institutional treatment, now supplemented by collapse therapy in pulmonary tuberculosis. Reports have been assembled for illustrative purposes from places far apart, New York City, Chicago, Philadelphia, Detroit and London; the states of New York, New Jersey

and Massachusetts as well as for England and Wales. They cover, generally for the twenty years between 1915 and 1935, the registration of tuberculosis cases and the mortality returns during the same period.

### TUBERCULOSIS REGISTRATION, VALUE AND LIMITATIONS

Before referring to the specific reports it might be wise to outline the limitations as well as the possible value of the registration of tuberculosis and the comparability of the figures during these years. In the main, even though it is acknowledged that many cases of tuberculosis are not reported or identified until near the end or at death, there are several reasons or factors making for a rather thorough registration of this disease, or for the reporting of cases more frequently now than formerly. First, the extensive provision of institutional facilities assures almost automatically that at least the cases going through them will at some time or other be reported to the authorities, either when applying or when caught in the meshes of the follow-up systems. Second, the frequency nowadays of special surveys for tuberculin-testing and case-finding also assures the recognition of a greater number of cases. Third, many large industrial and business establishments as well as civil service commissions now require physical examinations prior to employment, leading thereby to the identification of cases. Finally, the availability and wider use of the X-ray these days also contribute to the discovery of more cases than formerly. Then, too, the continuous search by visiting and public health nurses for possible contacts of tuberculosis cases uncovers many secondary cases. All of these channels of discovery or reporting should have as a net effect the raising of the total registration lately, and consequently the lowering of the ratio of deaths to cases. It is all the more surprising, therefore, in view of the many measures making for an increase of registration, to notice, as we shall see soon, the maintenance of rather stationary case fatality rates in tuberculosis.

As against the conditions just mentioned tending to enlarge the registration and, therefore, to decrease the case fatality ratio there may be at work and tending to produce a higher rate the following factors: first, some increase in deaths due to surgery—operative mortality; second, a greater proportion of colored patients especially in the American communities considered here. There may likewise be as a consequence of the more extensive use of surgery a tendency to keep patients in the cities and away from the older, conservative forms of treatment—open-air, hygienic-dietetic and rest in the country sanatoria. Instead, the

patients are retained in hospitals in town or in greater numbers at home under care of private physicians. Furthermore, with resort to collapse therapy in pulmonary tuberculosis there is a temptation to allow patients to return too quickly to work when the activity of the disease may not really have been brought under control and insufficient time given for lesions to heal.

On the contrary and making perhaps for lower fatality rates is the fact that as time goes on, between selection, immunization and acclimatization, more resistant types are developed; also, we have now in the United States, with the limitation of immigration, a greater proportion of the native-born and fewer ill adapted foreign groups.

## CASE FATALITY RATES

Disregarding increases of population and case or death rates in relation to the entire community, it is interesting to note, in New York City (table 1), for instance, in 1915, when 22,141 new cases of pulmonary tuberculosis were reported, that there were 8,825 deaths and, therefore, a ratio of deaths to cases of 40 per cent. In 1935, when cases numbered less, namely, 8,796 and the deaths 3,968, we still had 45 deaths to every 100 cases. For the three-year period 1915–1917, the case fatality rate was 44 per cent and two decades later, during the recent three-year period 1933–1935, it was still 42 per cent.[3]

Chicago (table 1) in 1915 had 12,709 tuberculosis cases and 4,204 deaths, the ratio of deaths to reported new cases then standing at 33 per cent; in 1935, even though the cases and the deaths had declined tremendously, there was still for every 100 new cases of tuberculosis a mortality of 33. Comparing the ratio in the three-year period 1915–1917 against that of the three years 1933–1935, we find the case fatality had risen from 30 to 35 per cent.

Figures are available, as reported for Detroit in table 2. They show a decline in the ratios of deaths to cases from 43 to 38 between the years 1915 and 1935. In that community, however, there has been a variety

[3] Since New York City led, under Biggs, in the registration of tuberculosis, a longer record of it is available there. In 1905, 20,831 new cases of, and 8,535 deaths from, pulmonary tuberculosis were reported, indicating then a fatality ratio of 41 per cent. At that time there were less than two thousand beds available in local tuberculosis hospitals; only a fraction of the total number of patients in 1905 (new cases of that year, and old ones carried over from former years) could receive institutional care. Practically speaking, these days were still in the presanatorium era; and yet the case fatality rate was apparently no different then than now.

of special campaigns and at times an inclusion into the registration of the childhood type of tuberculosis, which should be kept separate and never included with the frank or manifest cases of tuberculosis.

TABLE 2

*Tuberculosis, Detroit, Philadelphia—ratio of deaths to reported new cases*

| YEAR OR PERIOD | DETROIT* (PULMONARY) | | PHILADELPHIA† (ALL FORMS) | | YEAR OR PERIOD |
|---|---|---|---|---|---|
| | Cases‡ | Deaths | Cases | Deaths | |
| 1915 | 1,517 | 650 = 43% | 6,289 | 3,088 = 49% | 1915 |
| 1916 | 1,467 | 790 = 54% | 6,191 | 3,267 = 53% | 1916 |
| 1917 | 1,783 | 827 = 46% | 5,326 | 3,381 = 63% | 1917 |
| 1918 | 1,922 | 941 = 49% | 5,555 | 3,716 = 67% | 1918 |
| 1919 | 2,092 | 755 = 36% | 4,998 | 2,923 = 58% | 1919 |
| 1920 | 2,077 | 850 = 41% | 3,913 | 2,509 = 64% | 1920 |
| 1921 | 2,080 | 736 = 35% | 3,632 | 2,167 = 60% | 1921 |
| 1922 | 2,263 | 790 = 35% | 3,559 | 2,162 = 61% | 1922 |
| 1923 | 2,234 | 855 = 38% | 3,674 | 2,122 = 58% | 1923 |
| 1924 | 2,265 | 931 = 41% | 3,569 | 2,026 = 57% | 1924 |
| 1925 | 2,338 | 941 = 40% | 3,200 | 2,002 = 63% | 1925 |
| 1926 | 2,473 | 1,031 = 42% | 2,851 | 1,928 = 68% | 1926 |
| 1927 | 2,182 | 1,023 = 47% | 3,144 | 1,740 = 55% | 1927 |
| 1928 | 2,793 | 1,096 = 39% | 2,938 | 1,742 = 59% | 1928 |
| 1929 | 3,006 | 1,116 = 37% | 2,724 | 1,671 = 61% | 1929 |
| 1930 | 3,257 | 1,082 = 33% | 2,696 | 1,590 = 59% | 1930 |
| 1931 | 3,554 | 963 = 27% | 2,728 | 1,634 = 60% | 1931 |
| 1932 | 3,095 | 890 = 29% | 2,415 | 1,392 = 58% | 1932 |
| 1933 | 3,351 | 868 = 26% | 2,538 | 1,378 = 54% | 1933 |
| 1934‡ | 2,225 | 806 = 36% | 2,600 | 1,442 = 55% | 1934 |
| 1935‡ | 2,062 | 787 = 38% | 2,236 | 1,238 = 55% | 1935 |
| 1915–16 | 2,984 | 1,440 = 48% | 17,806 | 9,736 = 55% | 1915–17 |
| 1934–35 | 4,287 | 1,593 = 37% | 7,374 | 4,039 = 55% | 1933–35 |

* Reports by courtesy of Tuberculosis Controller, Department of Health, City of Detroit.

† Figures by courtesy, Division of Tuberculosis, Bureau of Health, Philadelphia.

‡ For the years 1934 and 1935 cases reported are "corrected for adult type only;" previously, cases of the childhood type of pulmonary tuberculosis are obviously included for an indefinite period.

In Philadelphia (table 2) between 1915 and 1935 the new cases have fallen from 6,289 to 2,236 and the deaths from 3,088 to 1,238. The ratio of deaths to cases, which stood at 55 per cent during the three-year period 1915–1917, was still the same during the years 1933 to 1935.

For the State of New York, exclusive of the City, (table 3) the ratio of deaths to cases has come down between the same three-year periods mentioned from 53 per cent to 49 per cent. In New Jersey (table 3) the

TABLE 3

*Tuberculosis, New York, New Jersey—ratio of deaths to reported new cases*

| YEAR OR PERIOD | NEW YORK STATE* (EXCLUSIVE OF NEW YORK CITY) (PULMONARY) | | STATE OF NEW JERSEY† (ALL FORMS) | | YEAR OR PERIOD |
|---|---|---|---|---|---|
| | Cases | Deaths | Cases‡ | Deaths | |
| 1915 | 9,950 | 5,404 = 54% | 8,490 | 4,371 = 51% | 1915 |
| 1916 | 10,580 | 5,406 = 51% | 9,017 | 4,333 = 48% | 1916 |
| 1917 | 10,666 | 5,675 = 53% | 8,177 | 4,617 = 56% | 1917 |
| 1918 | 9,552 | 6,079 = 64% | 7,943 | 4,739 = 60% | 1918 |
| 1919 | 10,082 | 5,279 = 52% | 7,460 | 3,820 = 51% | 1919 |
| 1920 | 8,940 | 4,761 = 53% | 6,055 | 3,625 = 60% | 1920 |
| 1921 | 8,118 | 4,264 = 53% | 5,255 | 3,041 = 58% | 1921 |
| 1922 | 8,294 | 4,238 = 51% | 5,642 | 3,175 = 56% | 1922 |
| 1923 | 8,600 | 4,360 = 51% | 5,613 | 3,046 = 54% | 1923 |
| 1924 | 8,189 | 4,239 = 52% | 4,938 | 2,997 = 61% | 1924 |
| 1925 | 7,984 | 4,230 = 53% | 4,984 | 2,907 = 58% | 1925 |
| 1926 | 7,405 | 4,104 = 55% | 5,371 | 3,093 = 58% | 1926 |
| 1927 | 7,403 | 3,830 = 52% | 5,196 | 2,830 = 54% | 1927 |
| 1928 | 7,817 | 3,864 = 49% | 4,983 | 2,862 = 57% | 1928 |
| 1929 | 7,487 | 3,802 = 51% | 5,223 | 2,917 = 56% | 1929 |
| 1930 | 7,298 | 3,536 = 48% | 5,306 | 2,805 = 53% | 1930 |
| 1931 | 6,786 | 3,359 = 49% | 5,249 | 2,702 = 51% | 1931 |
| 1932 | 6,564 | 3,207 = 49% | 4,540 | 2,569 = 57% | 1932 |
| 1933 | 6,297 | 3,018 = 48% | 4,461 | 2,376 = 53% | 1933 |
| 1934 | 5,748 | 2,911 = 51% | 4,094 | 2,230 = 54% | 1934 |
| 1935 | 5,765 | 2,839 = 49% | 4,296 | 2,143 = 50% | 1935 |
| 1915–17 | 31,196 | 16,485 = 53% | 25,684 | 13,321 = 52% | 1915–17 |
| 1933–35 | 17,810 | 8,768 = 49% | 12,851 | 6,749 = 53% | 1933–35 |

* From reports by courtesy, Division of Tuberculosis, Department of Health, State of New York.

† From reports, Department of Health, State of New Jersey.

‡ In 1915 figures are for the twelve months ending October 31; thereafter, for calendar year.

case fatality has remained practically identical, namely 52 per cent formerly and 53 per cent now; in Massachusetts (table 4) it has remained exactly at the same level, 54 per cent.

If we study likewise the comprehensive and perhaps more strictly comparable figures for all of England and Wales (table 4), where tuberculosis schemes have been centralized and reports standardized, we notice, during

TABLE 4

*Tuberculosis, Massachusetts, England and Wales—ratio of deaths to reported new cases*

| YEAR OR PERIOD | COMMONWEALTH OF MASSACHUSETTS* (PULMONARY) | | ENGLAND AND WALES† (PULMONARY) | | YEAR OR PERIOD |
|---|---|---|---|---|---|
| | Cases | Deaths | Cases‡ | Deaths | |
| 1915 | 8,046 | 4,194 = 52% | 68,309 | 40,803 = 60% | 1915 |
| 1916 | 7,878 | 4,467 = 57% | 68,109 | 40,769 = 60% | 1916 |
| 1917 | 8,365 | 4,559 = 55% | 68,801 | 42,335 = 60% | 1917 |
| 1918 | 7,833 | 5,078 = 65% | 71,631 | 45,338 = 63% | 1918 |
| 1919 | 6,977 | 4,145 = 59% | 61,154 | 35,984 = 59% | 1919 |
| 1920 | 6,696 | 3,645 = 54% | 57,844 | 32,791 = 57% | 1920 |
| 1921 | 6,168 | 3,272 = 53% | 56,334 | 33,505 = 60% | 1921 |
| 1922 | 5,562 | 3,167 = 57% | 53,422 | 33,919 = 64% | 1922 |
| 1923 | 5,356 | 3,062 = 57% | 59,172‡ | 32,097 = 54% | 1923 |
| 1924 | 5,376 | 2,953 = 55% | 60,747‡ | 32,690 = 54% | 1924 |
| 1925 | 5,385 | 2,883 = 54% | 60,770‡ | 32,382 = 54% | 1925 |
| 1926 | 5,444 | 2,961 = 54% | 59,520‡ | 30,108 = 51% | 1926 |
| 1927 | 5,049 | 2,774 = 55% | 58,109‡ | 31,066 = 53% | 1927 |
| 1928 | 4,873 | 2,690 = 55% | 57,682‡ | 29,799 = 52% | 1928 |
| 1929 | 4,538 | 2,561 = 56% | 57,274‡ | 31,425 = 55% | 1929 |
| 1930 | 4,696 | 2,423 = 52% | 54,331‡ | 29,414 = 54% | 1930 |
| 1931 | 4,421 | 2,306 = 52% | 54,596‡ | 29,658 = 54% | 1931 |
| 1932 | 3,994 | 2,041 = 51% | 51,836‡ | 27,627 = 53% | 1932 |
| 1933 | 3,541 | 2,059 = 58% | 49,958‡ | 27,854 = 56% | 1933 |
| 1934 | 3,585 | 1,902 = 53% | 48,208‡ | 25,682 = 53% | 1934 |
| 1935 | 3,594 | 1,814 = 50% | 45,015‡ | 24,603 = 55% | 1935 |
| 1915–17 | 24,289 | 13,220 = 54% | 180,689 | 97,169 = 54% | 1923–25 |
| 1933–35 | 10,720 | 5,775 = 54% | 143,181 | 78,139 = 55% | 1933–35 |

* From reports by courtesy, Division of Tuberculosis, Department of Public Health, Commonwealth of Massachusetts.

† From reports, Chief Medical Officer, Ministry of Health, England and Wales.

‡ From 1915 to 1922 inclusive, figures refer to "primary" notifications only; beginning in 1923 and thereafter they include "supplemental" returns, namely, cases identified from death certificates and other sources.

the period when only primary notifications were considered, namely, from 1915 to 1922, that the case fatality actually rose from 60 per cent to 64 per cent. But, during the succeeding period, 1923–1935, when the cases

reported included those in the supplementary returns, namely, cases identified from death certificates, etc., the ratio has remained practically unchanged, being 54 per cent at first and 55 per cent now.

### VARIATIONS IN TUBERCULOSIS REGISTRATION

Before commenting upon these reports, a word might be said to explain the apparent differences in case fatality rates in various places and that these do not necessarily invalidate the main point for consideration, namely, the constancy of the ratios rather than their levels. Reasons for variations probably include the following: first of all, a lack of uniformity perhaps in the requirements for registration and facilities for the recognition or discovery of cases in different places; second, within the same community an irregular or growing practice of including supplementary cases found through identification from death certificates and other sources. Or again, at certain periods an increase of registration due to special surveys among particular groups of the population, families on relief, or colored sections, and so on. Another factor may arise from material differences in the proportion of, changes or increases in, some particularly susceptible groups with higher mortality rates, such as Puerto Ricans and Mexicans. But, this is less apt to be true in countries with a homogeneous population such as in England. Differences in the level of registration may be due, as already mentioned, to unusual attention to the childhood type of tuberculosis. Finally, the ratio of deaths to cases may vary between communities if in certain ones all of the mortality takes place within the town limits and, in others, a goodly share occurs in out-of-town institutions.

### DECLINE OF TUBERCULOSIS

But in the reports presented here of deaths and cases, and their ratio, certain outstanding common facts are to be noted. First, of course, as well known, from either the angle of the absolute number of cases or of deaths marked declines have taken place practically everywhere (table 5). During the twenty years from 1915 to 1935, in New York City, the number of new cases fell by 60 per cent and the deaths by 55 per cent; but the case fatality rate actually rose from 40 to 45 per cent and, therefore, a given hundred cases of tuberculosis in 1935 suffered as high a mortality as the same number in the year 1915.

In Chicago, during the last twenty years, the cases fell in number by 54 per cent; the deaths likewise; but the fatality of the disease remained

the same, 33 out of a hundred cases both in 1915 and in 1935. Detroit, with its tremendous growth of population, shows increases in both the number of cases and deaths during the past twenty years, but a change in the fatality ratio of only 5 per cent. In Philadelphia, the cases declined by 64 per cent and the deaths by 60 per cent; the fatality increased by 6 per cent. In "up-State" New York, in the State of New Jersey, in Massachusetts, in England and Wales, the cases fell in number anywhere between 42 and 55 per cent and the deaths practically likewise, between 40 and 57 per cent; but the seriousness of the disease there, too, remains practically unchanged.

TABLE 5

*Tuberculosis cases, deaths and case fatality in 1915 and in 1935 compared*

| PLACE | NEW CASES REPORTED | | | NUMBER OF DEATHS | | | CASE FATALITY | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1915 | 1935 | Change | 1915 | 1935 | Change | 1915 | 1935 | Change |
| New York City* | 22,141 | 8,796 | Dec. 60% | 8,825 | 3,968 | Dec. 55% | 40% | 45% | Inc. 5% |
| Chicago† | 12,709 | 5,834 | Dec. 54% | 4,204 | 1,946 | Dec. 54% | 33% | 33% | None |
| Detroit* | 1,517 | 2,062 | Inc. 36% | 650 | 787 | Inc. 21% | 43% | 38% | Dec. 5% |
| Philadelphia† | 6,289 | 2,236 | Dec. 64% | 3,088 | 1,238 | Dec. 60% | 49% | 55% | Inc. 6% |
| "Up-State" N.Y.* | 9,950 | 5,765 | Dec. 42% | 5,404 | 2,839 | Dec. 47% | 54% | 49% | Dec. 5% |
| New Jersey† | 8,490 | 4,296 | Dec. 49% | 4,371 | 2,143 | Dec. 51% | 51% | 50% | Dec. 1% |
| Massachusetts* | 8,046 | 3,594 | Dec. 55% | 4,194 | 1,814 | Dec. 57% | 52% | 50% | Dec. 2% |
| England and Wales* | 68,309‡ | 39,635‡ | Dec. 42% | 40,803 | 24,603 | Dec. 40% | 60% | 62% | Inc. 2% |

* Pulmonary cases.
† All forms.
‡ "Primary notifications" only.

In 1924, in twenty-three states and eleven cities with a total population of 64,747,088, the reports to the United States Public Health Service show that there were registered in that year 108,662 cases of tuberculosis (2). The same year in these places there were 60,139 tuberculosis deaths, the registration being therefore 1.81 cases for each death or a case fatality ratio of 55 per cent.

In 1935, according to the special report of the National Tuberculosis Association from state departments of health on new cases, there were in the United States a total of 111,856 new cases of tuberculosis registered and at the same time 69,471 deaths, or 1.61 cases for each death and a

case fatality ratio of 62 per cent. In 1936, the mortality rose to 64 per cent.

And yet, it is in recent years particularly that there has become available and been utilized by an increasing number of patients, and by a greater proportion of all of the tuberculous population, sanatorium treatment and chest surgery. Further on, we will return to the question in mind of testing sanatorium treatment and its influence more directly with only the cases concerned, but let it be said that most of such studies have limited themselves to the immediate results of treatment and are an incorrect or incomplete measure; they should deal rather with the ultimate results. The difficulty, however, of tracing sanatorium patients and the existence already of quite a number of adequate investigations suggest that there is perhaps a greater finality and completeness in the community's record, rather than in those of the hospitals alone, for appraising the influence of the sanatorium and surgical treatment of tuberculosis.

## SURVIVAL IN TUBERCULOSIS

The trend of the case fatality in tuberculosis has been studied from a slightly different angle (table 6) for the State of New York and for England and Wales, where the probable number of survivors has been figured out during the period between 1913 and 1935 for the former, and during the period 1923–1935 for the latter place. On the assumption that the majority of the deaths from tuberculosis occur within two years, their number has been compared with the cases reported two years previously, and the ratio of the probable number of survivors then computed. In the State of New York, for instance, the proportion of survivors in 1915 to the cases reported in 1913 was around 53 per cent; in 1935 it was slightly higher, 58 per cent. In England and Wales, only the period 1923 to 1935 has been considered because starting from the first year mentioned consideration was given to the so-called "supplemental" returns; at the beginning, the proportion of survivors was 45 per cent; in 1935, it was higher, around 51 per cent.

## CASE FATALITY ACCORDING TO AGE AND SEX

Granting the comparative constancy of the fatality rates in tuberculosis, the point has been made that differences are perhaps masked by important changes in the age composition of the tuberculosis cases now from formerly. Though it has been difficult to get at representative

## TABLE 6

*Annual deaths from pulmonary tuberculosis in relation to new cases reported two years previously, and probable survivors**

I.—State of New York†, Period 1913–1935

| | 1913 C. 1915 D. | 1914 C. 1916 D. | 1915 C. 1917 D. | 1916 C. 1918 D. | 1917 C. 1919 D. | 1918 C. 1920 D. | 1919 C. 1921 D. |
|---|---|---|---|---|---|---|---|
| New cases reported | 31,123 | 30,905 | 32,091 | 29,872 | 28,080 | 23,891 | 24,652 |
| Deaths 2 years later | 14,512 | 14,069 | 14,795 | 15,052 | 12,814 | 11,030 | 9,407 |
| Survivors, probable | 16,611 | 16,836 | 17,296 | 14,820 | 15,266 | 12,861 | 15,245 |
| Proportion | 53% | 54% | 54% | 50% | 54% | 54% | 62% |
| | 1920 C. 1922 D. | 1921 C. 1923 D. | 1922 C. 1924 D. | 1923 C. 1925 D. | 1924 C. 1926 D. | 1925 C. 1927 D. | 1926 C. 1928 D. |
| New cases reported | 22,975 | 21,084 | 21,623 | 19,936 | 20,113 | 18,939 | 17,903 |
| Deaths 2 years later | 9,394 | 9,443 | 9,177 | 9,143 | 9,095 | 8,435 | 8,667 |
| Survivors, probable | 13,581 | 11,641 | 12,446 | 10,793 | 11,018 | 10,504 | 9,236 |
| Proportion | 59% | 55% | 58% | 54% | 55% | 55% | 52% |
| | 1927 C. 1929 D. | 1928 C. 1930 D. | 1929 C. 1931 D. | 1930 C. 1932 D. | 1931 C. 1933 D. | 1932 C. 1934 D. | 1933 C. 1935 D. |
| New cases reported | 18,276 | 19,431 | 19,425 | 19,119 | 18,580 | 17,153 | 16,288 |
| Deaths 2 years later | 8,516 | 8,146 | 7,833 | 7,354 | 7,192 | 6,983 | 6,847 |
| Survivors, probable | 9,760 | 11,285 | 11,592 | 11,765 | 11,388 | 10,170 | 9,441 |
| Proportion | 53% | 58% | 60% | 62% | 61% | 59% | 58% |

II.—England and Wales‡, Period 1923–1935

| | 1923 C. 1925 D. | 1924 C. 1926 D. | 1925 C. 1927 D. | 1926 C. 1928 D. |
|---|---|---|---|---|
| New cases¶ reported | 59,172 | 60,747 | 60,770 | 59,520 |
| Deaths 2 years later | 32,382 | 30,108 | 31,066 | 29,799 |
| Survivors, probable | 26,790 | 30,639 | 29,704 | 29,721 |
| Proportion | 45% | 50% | 49% | 50% |

| | 1927 C. 1929 D. | 1928 C. 1930 D. | 1929 C. 1931 D. | 1930 C. 1932 D. | 1931 C. 1933 D. | 1932 C. 1934 D. | 1933 C. 1935 D. |
|---|---|---|---|---|---|---|---|
| New cases¶ reported | 58,109 | 57,682 | 57,274 | 54,331 | 54,596 | 51,836 | 49,958 |
| Deaths 2 years later | 31,425 | 29,414 | 29,658 | 27,627 | 27,854 | 25,682 | 24,603 |
| Survivors, probable | 26,684 | 28,268 | 27,616 | 26,704 | 26,742 | 26,154 | 25,355 |
| Proportion | 46% | 49% | 48% | 49% | 49% | 50% | 51% |

* On assumption that most deaths occur within two years from reporting of the case.

† Based on reports, Department of Health, State of New York.

‡ Based on reports, Chief Medical Officer, Ministry of Health.

¶ Beginning in 1923, cases include those identified from death certificates and other supplementary sources.

material especially for former years, the age composition of tuberculosis cases lately and some time ago has also been studied. In table 7 for the three cities of New York, Chicago and London, and the larger areas of New York State, New Jersey, England and Wales, the case fatality according to age and sex, during the two-year period 1933–1934, has been calculated. The level of the ratios is naturally dependent upon the thoroughness of registration in the various places, but within a certain range they do not differ materially as to their trends. In particular, they have certain common characteristics with regard to the influence of age.

In New York City, during the two-year period just mentioned, the ratio of deaths to cases was approximately, for both sexes, 42 per cent; in Chicago, 36 per cent; in London, 45 per cent; in "up-State" New York, 48 per cent; in New Jersey, where obviously the registration of cases has not been quite as complete as in the other places, 54 per cent; and, in England and Wales, 49 per cent. In general, the ratio of deaths to cases is higher in the male than in the female sex. But, after noting the higher mortality rate of children under five years of age and the comparatively lower rate in the age group five to fifteen, it will be remarked that everywhere the case fatality increases directly with advancing age. In other words, if there were marked differences in the age composition of the tuberculous group formerly and now, the crude case fatality rate of the entire community would be correspondingly affected. It is doubtful, however, whether, during the twenty-year period under consideration, changes in the age composition of the tuberculous have been extensive enough to be responsible for the comparative maintenance of the fatality rates noted in the places studied by hiding possible improvements that would otherwise have become apparent.

In the United States particularly, because of the greater gains made against tuberculosis in children, there has been indeed some change in the age composition of the tuberculous population. Also, in the American communities listed here there has been an increasing proportion of colored in the tuberculous groups.

In default of information as to the age of registered cases formerly or now for all of the places studied, resort has had to be made to the age distribution as ascertainable from the mortality records except for New Jersey and "up-State" New York where information on cases reported ten years or so ago is at hand.

## TABLE 7

I.—*New York City*†—*Tuberculosis (all forms), two-year period 1933–1934—Case fatality according to age and sex*

| AGE | NEW CASES‡ | | | RATIO OF DEATHS TO CASES | | | DEATHS‡ | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 323 | 293 | 616 | 57.6% | 53.2% | 55.5% | 342 | 156 | 186 | 0– 4 |
| 5–14 | 392 | 421 | 813 | 24.5% | 25.2% | 24.8% | 202 | 106 | 96 | 5–14 |
| 15–24 | 1,788 | 2,270 | 4,058 | 32.7% | 35.9% | 34.5% | 1,400 | 816 | 584 | 15–24 |
| 25–44 | 5,923 | 3,629 | 9,552 | 40.3% | 39.3% | 39.9% | 3,812 | 1,425 | 2,387 | 25–44 |
| 45–64 | 3,624 | 1,180 | 4,804 | 57.2% | 49.7% | 55.3% | 2,658 | 586 | 2,072 | 45–64 |
| 65+ | 555 | 284 | 839 | 70.5% | 67.6% | 69.5% | 583 | 192 | 391 | 65+ |
| Unknown | 478 | 333 | 811 | | | | | | | Unknown |
| Total | 13,083 | 8,410 | 21,493 | 43.7% | 39.0% | 41.9% | 8,997 | 3,281 | 5,716 | Total |

Note: Cases include those identified from death certificates.

† Population, July 1, 1934: 7,226,164.

‡ Based upon reports, bureaus of Tuberculosis and of Records, Department of Health, City of New York.

II.—*Chicago*†—*Tuberculosis (all forms), two-year period 1933–1934—Case fatality according to age and sex*

| AGE | NEW CASES‡ | | | RATIO OF DEATHS TO CASES | | | DEATHS‡ | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 209 | 181 | 390 | 34.4% | 38.1% | 36.2% | 141 | 69 | 72 | 0– 4 |
| 5–14 | 506 | 582 | 1,088 | 11.5% | 13.2% | 12.4% | 135 | 77 | 58 | 5–14 |
| 15–24 | 929 | 1,407 | 2,336 | 32.4% | 33.8% | 33.2% | 776 | 475 | 301 | 15–24 |
| 25–34 | 1,321 | 1,323 | 2,644 | 39.4% | 34.8% | 37.1% | 980 | 460 | 520 | 25–34 |
| 35–44 | 1,405 | 631 | 2,036 | 36.8% | 41.0% | 38.1% | 776 | 259 | 517 | 35–44 |
| 45–64 | 1,602 | 472 | 2,074 | 49.3% | 48.9% | 49.2% | 1,020 | 231 | 789 | 45–64 |
| 65+ | 182 | 72 | 254 | 58.2% | 61.1% | 59.1% | 150 | 44 | 106 | 65+ |
| Unknown | 168 | 76 | 244 | | | | | | | |
| Total | 6,322 | 4,744 | 11,066 | 37.4% | 34.0% | 35.9% | 3,978 | 1,615 | 2,363 | Total |

Note: Cases include those identified from death certificates.

† Population, July 1, 1934: 3,490,700.

‡ Based upon reports of the Municipal Tuberculosis Sanitarium, City of Chicago.

TABLE 7—*Continued*

III.—*London*†—*Tuberculosis (all forms), two-year period 1933–1934—Case fatality according to age and sex*

| AGE | NEW CASES‡ NOTIFIED | | | RATIO OF DEATHS TO CASES | | | DEATHS‡ | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 357 | 301 | 658 | 42.9% | 44.5% | 43.6% | 287 | 134 | 153 | 0– 4 |
| 5–14 | 829 | 727 | 1,556 | 14.4% | 17.6% | 15.9% | 247 | 128 | 119 | 5–14 |
| 15–24 | 2,032 | 2,454 | 4,486 | 33.6% | 34.8% | 34.3% | 1,537 | 854 | 683 | 15–24 |
| 25–34 | 2,041 | 1,942 | 3,983 | 43.3% | 38.8% | 41.1% | 1,638 | 754 | 884 | 25–34 |
| 35–44 | 1,494 | 891 | 2,385 | 50.1% | 46.9% | 48.9% | 1,166 | 418 | 748 | 35–44 |
| 45–54 | 1,499 | 553 | 2,052 | 66.3% | 59.3% | 64.4% | 1,322 | 328 | 994 | 45–54 |
| 55–64 | 1,025 | 347 | 1,372 | 75.1% | 63.1% | 72.1% | 989 | 219 | 770 | 55–64 |
| 65+ | 392 | 183 | 575 | 88.3% | 79.8% | 85.6% | 492 | 146 | 346 | 65+ |
| Total | 9,669 | 7,398 | 17,067 | 48.6% | 40.3% | 45.0% | 7,678 | 2,981 | 4,697 | Total |

Note: Cases include those identified from death certificates.

† Administrative County of London, population, July 1, 1934: 4,230,200.

‡ Data based upon reports of the London County Medical Officer of Health, and of the Registrar-General of England and Wales.

IV.—*New York State*† *(exclusive of New York City)—Tuberculosis (all forms), two-year period 1933–1934—Case fatality according to age and sex*

| AGE | NEW CASES‡ | | | RATIO OF DEATHS TO CASES | | | DEATHS‡ | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 179 | 138 | 317 | 48.6% | 45.7% | 47.3% | 150 | 63 | 87 | 0– 4 |
| 5–14 | 588 | 656 | 1,244 | 10.0% | 7.8% | 8.8% | 110 | 51 | 59 | 5–14 |
| 15–24 | 1,002 | 1,616 | 2,618 | 33.3% | 31.4% | 32.1% | 841 | 507 | 334 | 15–24 |
| 25–34 | 1,417 | 1,530 | 2,947 | 45.7% | 43.1% | 44.4% | 1,307 | 660 | 647 | 25–34 |
| 35–44 | 1,577 | 852 | 2,429 | 61.5% | 52.2% | 58.3% | 1,415 | 445 | 970 | 35–44 |
| 45–54 | 1,286 | 534 | 1,820 | 64.5% | 64.8% | 64.6% | 1,175 | 346 | 829 | 45–54 |
| 55–64 | 767 | 334 | 1,101 | 73.3% | 68.6% | 71.8% | 791 | 229 | 562 | 55–64 |
| 65+ | 439 | 273 | 712 | 85.4% | 94.5% | 88.9% | 633 | 258 | 375 | 65+ |
| Unknown | 49 | 58 | 107 | | | | | | | |
| Total | 7,304 | 5,991 | 13,295 | 52.9% | 42.7% | 48.3% | 6,422 | 2,559 | 3,863 | Total |

Note: Cases include those identified from death certificates.

† Population, July 1, 1934: 5,880,649.

‡ Based upon reports, divisions of Vital Statistics and of Tuberculosis, New York State Department of Health.

TABLE 7—*Concluded*

V.—*State of New Jersey*†—*Tuberculosis (all forms), two-year period 1933–1934—Case fatality according to age and sex*

| AGE | NEW CASES‡ | | | RATIO OF DEATHS TO CASES | | | DEATHS‡ | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 94 | 69 | 163 | 60.6% | 87.0% | 71.8% | 117 | 60 | 57 | 0– 4 |
| 5–14 | 356 | 370 | 726 | 9.6% | 16.8% | 13.2% | 96 | 62 | 34 | 5–14 |
| 15–24 | 725 | 1,101 | 1,826 | 43.7% | 39.1% | 40.9% | 747 | 430 | 317 | 15–24 |
| 25–34 | 1,035 | 1,038 | 2,073 | 46.6% | 50.9% | 48.9% | 1,011 | 529 | 482 | 25–34 |
| 35–44 | 994 | 584 | 1,578 | 56.5% | 57.0% | 56.7% | 895 | 333 | 562 | 35–44 |
| 45–54 | 845 | 294 | 1,139 | 73.5% | 75.9% | 74.1% | 844 | 223 | 621 | 45–54 |
| 55–64 | 548 | 193 | 741 | 75.4% | 86.5% | 78.3% | 580 | 167 | 413 | 55–64 |
| 65+ | 195 | 114 | 309 | 97.9% | 109.6% | 102.3% | 316 | 125 | 191 | 65+ |
| Total | 4,792 | 3,763 | 8,555 | 55.9% | 51.3% | 53.8% | 4,606 | 1,929 | 2,677 | Total |

Note: Cases do not include those identified from death certificates.

† Population, July 1, 1934: 4,231,000.

‡ Based upon reports, bureaus of Local Health Administration and of Vital Statistics, New Jersey State Department of Health.

VI.—*England and Wales*†—*Tuberculosis (all forms), deaths and cases*‡, *two-year period 1933–1934—Case fatality according to age and sex*

| AGE | DEATHS | | | RATIO OF DEATHS TO CASES | | | NEW CASES‡ NOTIFIED | | | AGE |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Both sexes | Total | Female | Male | |
| 0– 4 | 1,977 | 1,632 | 3,609 | 44.9% | 46.8% | 45.7% | 7,891 | 3,489 | 4,402 | 0– 4 |
| 5–14 | 1,374 | 1,585 | 2,959 | 13.3% | 16.7% | 14.9% | 19,797 | 9,477 | 10,320 | 5–14 |
| 15–24 | 5,820 | 7,520 | 13,340 | 40.7% | 42.5% | 41.7% | 31,967 | 17,680 | 14,287 | 15–24 |
| 25–34 | 7,148 | 7,037 | 14,185 | 52.0% | 50.3% | 51.1% | 27,734 | 13,979 | 13,755 | 25–34 |
| 35–44 | 6,306 | 4,319 | 10,625 | 59.4% | 59.0% | 59.2% | 17,940 | 7,324 | 10,616 | 35–44 |
| 45–54 | 6,889 | 2,840 | 9,729 | 72.3% | 65.8% | 70.3% | 13,849 | 4,319 | 9,530 | 45–54 |
| 55–64 | 4,751 | 1,836 | 6,587 | 83.5% | 74.9% | 80.9% | 8,141 | 2,452 | 5,689 | 55–64 |
| 65+ | 1,917 | 1,190 | 3,107 | 98.3% | 90.7% | 95.2% | 3,262 | 1,311 | 1,951 | 65+ |
| Total | 36,182 | 27,959 | 64,141 | 51.3% | 46.6% | 49.1% | 130,581 | 60,031 | 70,550 | Total |

† England and Wales, population, July 1, 1934: 40,467,000.

‡ Including supplementary cases identified from death certificates. Data based upon reports of the Registrar-General, and figures of notifications by courtesy of the Chief Medical Officer, Ministry of Health.

AGE OF THE TUBERCULOUS, FORMERLY AND NOW

In New York City (table 8) during the twenty-year period 1914 to 1934, the proportion of tuberculosis deaths among persons under the age of twenty to the total dying from that cause has decreased from 17 per cent to 10 per cent; and the proportion of those fifty years of age and over has increased from 17 per cent to 27 per cent. Likewise, during the same period the proportion of the deaths of the colored has risen from 6.5 per cent to 23 per cent of the total mortality. In Chicago, the proportion of deaths in the younger age group does not seem to have varied materially during the past twenty years, being formerly 15 per cent of the total and now 14 per cent. But the proportion among the older persons, past fifty, has risen from 15 to 22 per cent. Also, the colored group there is now responsible for 33 per cent of the mortality as against 7 per cent formerly, and it may be recalled that there is an unusually high mortality from tuberculosis among young colored girls as compared with white girls.

In the State of New York, as in the City, there has been during the past twenty years a material decrease in the proportion of tuberculosis deaths of young people and an increase among the comparatively aged. In New Jersey a similar shift has taken place. In the United States Registration Area, in 1914, 17 per cent of the deaths were in the age group under twenty; and twenty years later, in 1934, in the entire United States this young group contributed 12 per cent of the mortality. As in New York and in New Jersey, the group fifty years and over likewise furnishes now in the United States a higher proportion of the deaths; also, the colored mortality has doubled its proportion from 14 to 30 per cent. In England and Wales, as here, there has been a fair decrease in the proportion of deaths suffered by the younger people and some increase, but not so marked as in the United States, in the deaths of persons past age fifty.

But the central adult age group, twenty to fifty years of age, has continued everywhere to contribute around two-thirds of the mortality with only fairly limited changes during the twenty-year period 1914 to 1934. In table 9, for all the places studied, there has been reduced to a comparable basis the age of the new cases reported during the two-year period 1933–1934, and that of all dying from tuberculosis during the same years; also, for "up-State" New York and New Jersey the changes in the average age of cases and of those dying recently and ten years previously, as well as that for England and Wales in 1914 and in 1935.

## TABLE 8

*Tuberculosis* deaths according to age, years 1914 and 1934 compared*

I

| AGE | NEW YORK CITY | | | | CHICAGO | | | | AGE |
|---|---|---|---|---|---|---|---|---|---|
| | 1914 | | 1934 | | 1914 | | 1934 | | |
| | Number of deaths | Proportion | Proportion | Number of deaths | Number of deaths | Proportion | Proportion | Number of deaths | |
| 0– 5 | 756 | 7.3% | 3.6% | 159 | 246 | 6.2% | 3.4% | 66 | 0– 5 |
| 5– 9 | 239 | 2.3% | 0.8% | 34 | 53 | 1.3% | 1.3% | 25 | 5– 9 |
| 10–19 | 770 | 7.5% | 5.4% | 243 | 284 | 7.2% | 8.9% | 173 | 10–19 |
| 20–29 | 2,113 | 20.5% | 22.2% | 980 | 1,074 | 27.2% | 24.2% | 471 | 20–29 |
| 30–39 | 2,536 | 24.7% | 20.9% | 925 | 978 | 24.8% | 21.1% | 411 | 30–39 |
| 40–49 | 2,140 | 20.8% | 20.0% | 882 | 731 | 18.5% | 19.4% | 377 | 40–49 |
| 50–59 | 1,148 | 11.2% | 15.6% | 689 | 417 | 10.5% | 13.2% | 256 | 50–59 |
| 60–69 | 465 | 4.5% | 8.4% | 370 | 134 | 3.4% | 6.7% | 130 | 60–69 |
| 70+ | 123 | 1.2% | 3.1% | 138 | 37 | 0.9% | 1.8% | 36 | 70+ |
| Total | 10,290 | 100.0% | 100.0% | 4,420 | 3,954 | 100.0% | 100.0% | 1,945 | Total |
| 0–19 | 1,765 | 17.1% | 9.8% | 436 | 583 | 14.7% | 13.6% | 264 | 0–19 |
| 20–50 | 6,789 | 66.0% | 63.1% | 2,787 | 2,783 | 70.5% | 64.7% | 1,259 | 20–50 |
| 50+ | 1,736 | 16.9% | 27.1% | 1,197 | 588 | 14.8% | 21.7% | 422 | 50+ |
| White | 9,617 | 93.5% | 77.1% | 3,408 | 3,668 | 92.8% | 67.3% | 1,309 | White |
| Colored | 673 | 6.5% | 22.9% | 1,012 | 286 | 7.2% | 32.7% | 636 | Colored |

II

| AGE | STATE OF NEW YORK | | | | STATE OF NEW JERSEY | | | | AGE |
|---|---|---|---|---|---|---|---|---|---|
| | 1914 | | 1934 | | 1914 | | 1934 | | |
| | Number of deaths | Proportion | Proportion | Number of deaths | Number of deaths | Proportion | Proportion | Number of deaths | |
| 0– 5 | 1,124 | 6.8% | 3.1% | 237 | 288 | 6.6% | 2.5% | 56 | 0– 5 |
| 5– 9 | 338 | 2.0% | 0.7% | 56 | 69 | 1.6% | 0.5% | 10 | 5– 9 |
| 10–19 | 1,297 | 7.8% | 5.6% | 425 | 355 | 8.2% | 6.7% | 148 | 10–19 |
| 20–29 | 3,702 | 22.2% | 20.4% | 1,549 | 1,016 | 23.3% | 22.2% | 493 | 20–29 |
| 30–39 | 3,941 | 23.7% | 21.0% | 1,593 | 1,083 | 24.9% | 20.4% | 452 | 30–39 |
| 40–49 | 3,190 | 19.2% | 20.8% | 1,584 | 767 | 17.6% | 20.2% | 447 | 40–49 |
| 50–59 | 1,829 | 11.0% | 15.3% | 1,163 | 478 | 11.0% | 14.0% | 311 | 50–59 |
| 60–69 | 881 | 5.3% | 8.7% | 660 | 197 | 4.5% | 9.7% | 214 | 60–69 |
| 70+ | 341 | 2.0% | 4.4% | 331 | 98 | 2.3% | 3.8% | 85 | 70+ |
| Total | 16,643 | 100.0% | 100.0% | 7,598 | 4,351 | 100.0% | 100.0% | 2,216 | Total |
| 0–19 | 2,759 | 16.6% | 9.4% | 718 | 712 | 16.4% | 9.7% | 214 | 0–19 |
| 20–50 | 10,833 | 65.1% | 62.2% | 4,726 | 2,866 | 65.8% | 62.8% | 1,392 | 20–50 |
| 50+ | 3,051 | 18.3% | 28.4% | 2,154 | 773 | 17.8% | 27.5% | 610 | 50+ |
| White | 15,758 | 94.7% | 83.0% | 6,304 | 3,973 | 91.3% | 77.9% | 1,727 | White |
| Colored | 885 | 5.3% | 17.0% | 1,294 | 378 | 8.7% | 22.1% | 489 | Colored |

* All forms of tuberculosis. Based on Mortality Statistics, U. S. Bureau of the Census.

TABLE 8—*Concluded*

III

| AGE | U. S. REGISTRATION AREA† | | UNITED STATES (CONTINENTAL) | | ENGLAND AND WALES‡ | | | | AGE |
|---|---|---|---|---|---|---|---|---|---|
| | 1914 | | 1934 | | 1914 | | 1934 | | |
| | Number of deaths | Proportion | Proportion | Number of deaths | Number of deaths | Proportion | Proportion | Number of deaths | |
| 0– 5 | 6,248 | 6.4% | 3.2% | 2,289 | 7,013 | 13.9% | 5.6% | 1,721 | 0– 5 |
| 5– 9 | 1,710 | 1.8% | 1.1% | 803 | 2,140 | 4.3% | 2.2% | 686 | 5– 9 |
| 10–19 | 8,457 | 8.7% | 7.7% | 5,548 | 5,836 | 11.6% | 9.9% | 3,062 | 10–19 |
| 20–29 | 24,536 | 25.3% | 22.3% | 15,980 | 9,267 | 18.4% | 24.9% | 7,690 | 20–29 |
| 30–39 | 21,556 | 22.2% | 19.8% | 14,132 | 9,611 | 19.1% | 18.7% | 5,775 | 30–39 |
| 40–49 | 15,551 | 16.1% | 17.5% | 12,517 | 7,875 | 15.7% | 15.8% | 4,856 | 40–49 |
| 50–59 | 9,842 | 10.2% | 13.4% | 9,577 | 5,226 | 10.4% | 13.6% | 4,198 | 50–59 |
| 60–69 | 5,782 | 6.0% | 9.1% | 6,514 | 2,567 | 5.1% | 7.2% | 2,235 | 60–69 |
| 70+ | 3,221 | 3.3% | 5.9% | 4,249 | 763 | 1.5% | 2.1% | 659 | 70+ |
| Total | 96,903 | 100.0% | 100.0% | 71,609 | 50,298 | 100.0% | 100.0% | 30,882 | Total |
| 0–19 | 16,415 | 16.9% | 12.0% | 8,640 | 14,989 | 29.8% | 17.7% | 5,469 | 0–19 |
| 20–50 | 61,643 | 63.6% | 59.6% | 42,629 | 26,753 | 53.2% | 59.4% | 18,321 | 20–50 |
| 50+ | 18,845 | 19.5% | 28.4% | 20,340 | 8,556 | 17.0% | 22.9% | 7,092 | 50+ |
| White | 83,243 | 85.9% | 70.5% | 50,510 | | | | | White |
| Colored | 13,660 | 14.1% | 29.5% | 21,099 | | | | | Colored |

† Based on Mortality Statistics, U. S. Bureau of the Census, the Registration Area covering in 1914, 67.2% of the population, and in 1934 the entire country.

‡ From Reports, the Registrar-General, England and Wales.

In general, the difference between the age of cases and the age "at death" —from which perhaps might be inferred the average life or duration of a case—was shorter among women than among men. In New York City, the average age of new cases reported recently is 39.1 years among males, 31.0 among females; and of those dying, 42 among the males and 33 among the females. In England and Wales, male cases average 31.2 years, female 27.5 years; and the deaths, nearly 38 years for males and 32 years for females.

For "up-State" New York, during the ten years between 1925 and 1935, from the data for new cases, it would seem that now as against formerly the male cases are older by 4.5 years, and the female by 2.1 years. In New Jersey between 1924 and 1934 the age of male cases has risen by less than two years (1.9) and that of female cases has remained almost the same (30.1 and 30.8). In England and Wales, during the

twenty-one years between 1914 and 1935[4] the average age of the cases "notified" has increased among males by only 3.3 years (from 27.9 to 31.2) and among females by just two years (from 25 to 27).

The differences noted between the age of cases or deaths now and formerly are not great enough to modify materially the fatality rates of the communities investigated.

TABLE 9

*Tuberculosis*—Age† of cases at time of reporting and at death—Two-year period 1933–34, etc.*

| PLACE | AVERAGE AGE OF NEW CASES REGISTERED | | AVERAGE AGE OF ALL DYING FROM TUBERCULOSIS | | DIFFERENCE BETWEEN AGE OF CASES AND OF THOSE WHO DIED | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| New York City | 39.1 | 31.0 | 42.0 | 33.4 | 2.9 | 2.4 |
| Chicago | 36.4 | 28.1 | 40.4 | 31.3 | 4.0 | 3.2 |
| London | 35.2 | 29.5 | 41.4 | 33.6 | 6.2 | 4.1 |
| "Up-State" New York | 38.6 | 31.5 | 44.3 | 38.4 | 5.7 | 6.9 |
| New Jersey | 38.1 | 30.7 | 43.3 | 35.7 | 5.2 | 5.0 |
| United States‡ | | | 41.5 | 35.8 | | |
| England and Wales | 31.2 | 27.5 | 37.8 | 32.1 | 6.1 | 4.6 |
| "Up-State" New York: | | | | | | |
| Year 1925 | 34.5 | 30.2 | 38.7 | 34.1 | 4.2 | 3.9 |
| Year 1935 | 39.0 | 32.3 | 44.4 | 38.6 | 5.4 | 6.3 |
| New Jersey: | | | | | | |
| Year 1924 | 34.8 | 30.1 | 38.5 | 31.6 | 3.7 | 1.5 |
| Year 1934 | 36.7 | 30.8 | 42.3 | 36.2 | 5.6 | 4.6 |
| United States: | | | | | | |
| 1913 (Reg. Area) | | | 36.4 | 32.5 | | |
| 1933 (entire) | | | 41.5 | 35.8 | | |
| England and Wales: | | | | | | |
| Year 1914 | 27.9 | 25.0 | 32.6 | 29.0 | 2.7 | 4.0 |
| Year 1935 | 31.2 | 27.0 | 38.9 | 32.8 | 7.7 | 5.8 |

* All forms of tuberculosis.

† Age in years.

‡ U. S. deaths for year 1933 only (cases not available). Based upon local figures of registration or "notification" of new cases and the total mortality returns of the various communities.

## RESULTS OF SANATORIUM TREATMENT

Passing from tuberculosis registration let us study some figures which may reveal the possible influence of institutional care upon the mortal-

[4] Based upon a personal communication by courtesy of Sir Arthur MacNalty, Chief Medical Officer, Ministry of Health.

ity returns. In the New York Metropolitan Area (table 10) reports are available for a large group of hospitals and sanatoria during the ten-year period 1927–1936; also, in a more limited way, for New York City as far back as twenty-seven years ago, in 1910. Likewise, the reports of the Chief Medical Officer of the Ministry of Health contain comprehensive figures of the mortality of patients in "approved residential institutions" in England during the ten-year period 1927–1936 (table 11).

In the New York Metropolitan Area, in 1927, 11,739 patients were discharged either alive or dead, the mortality ratio to the total dis-

TABLE 10

*New York and New Jersey Metropolitan Area—Mortality ratio of tuberculosis patients in hospitals and sanatoria—Ten-year period, 1927–1936**

| | 1927 | 1928 | 1929 | 1930 | 1931 | 1932 |
|---|---|---|---|---|---|---|
| Total discharged** | 11,739 | 12,778 | 13,827 | 15,454 | 16,869 | 16,830 |
| Died in institutions | 2,904 | 3,016 | 3,079 | 3,403 | 3,462 | 3,232 |
| Mortality ratio | 25% | 24% | 22% | 22% | 21% | 19% |

| | 1933 | 1934 | 1935 | 1936 | TEN YEARS 1927–36 |
|---|---|---|---|---|---|
| Total discharged** | 17,909 | 17,311 | 16,843 | 17,188 | 156,748 |
| Died in institutions | 3,321 | 3,273 | 3,228 | 3,577 | 32,495 |
| Mortality ratio | 19% | 19% | 19% | 21% | 21% |

* From reports submitted to the Tuberculosis Sanatorium Conference of Metropolitan New York by member institutions, 28 of them in 1927 with a bed capacity of 4,947 and 40 in 1936 with a capacity of 9,799 beds on December 31.

** Discharged alive or dead.

Note: In New York City institutions the mortality ratio was 29% in 1910 and 25% in 1917.

charges being 25 per cent that year. This has varied slightly each year and in 1936 it was down to 21 per cent. Twenty years ago, in 1917, in the New York institutions alone, according to unpublished reports[5] it was 25 per cent, the same as in 1927; and, in 1910, it was 29 per cent. But these figures do not show whether we are dealing with different types of cases now, whether they are in earlier or more advanced stages of disease than formerly. It is probable, however, as they are the all-inclusive reports for a very large area, and remembering the common complaint

[5] Tabulations by Frank H. Mann, of the Committee on Prevention of Tuberculosis of the Charity Organization Society.

that cases are still too frequently found in the advanced stages, that there is no very great variation in their character and that the results are fairly comparable. It is during that period, of course, that collapse therapy has come into wide use.

In the survey made by the writer in 1926 of tuberculosis hospitalization in the United States there became available reports from 134 institutions, which indicated that in the previous year there were discharged, alive or dead, 38,288 patients among whom 7,705, or 20 per cent,

TABLE 11

*England—Pulmonary tuberculosis "patients in approved residential institutions"—Mortality ratio during ten-year period, 1927–1936**

| | 1927 | 1928 | 1929 | 1930 | 1931 | 1932 |
|---|---|---|---|---|---|---|
| Total discharged** | 35,445 | 35,183 | 35,558 | 34,639 | 35,764 | 39,198 |
| Died in institutions | 3,981† | 4,321 | 4,544 | 4,471 | 4,882 | 6,457 |
| Mortality ratio | 11% | 12% | 13% | 13% | 14% | 16% |

| | 1933 | 1934 | 1935 | 1936 | TEN YEARS 1927–36 |
|---|---|---|---|---|---|
| Total discharged** | 39,889 | 37,505 | 38,122 | 39,455 | 370,758 |
| Died in institutions | 6,840 | 6,647 | 7,020 | 7,428 | 56,591 |
| Mortality ratio | 17% | 18% | 18% | 19% | 15% |

* From Annual Reports, Chief Medical Officer, Ministry of Health. On February 1, 1927, there were 22,202 beds in 482 approved institutions, and on December 31, 1935, a total of 28,020 beds.

** Discharged alive or dead.

† Deaths in institutions of pulmonary cases and of those "for observation" numbered 4,549; the former being usually seven-eighths of the total or nearly 3,981.

died. In 1931, Jessamine S. Whitney of the National Tuberculosis Association conducted a similar survey, and in 278 institutions reporting there were 42,156 patients discharged, alive or dead, the latter numbering 9,641, or 23 per cent. The survey of the American Medical Association (3), for the year 1933, covered 507 institutions with a total of 67,021 patients[6] discharged, alive or dead. The number who died in institutions was 16,041, a mortality ratio of 24 per cent. In other words, these broad surveys by three different authorities, covering most of the United States, reveal no improvement in recent years in the mortality ratio of the cases treated in sanatoria or hospitals.

In England (table 11) the institutional record for pulmonary cases

[6] Adult type of tuberculosis only.

shows no betterment during the ten-year period 1927–1936, but instead a rising fatality rate. In 1927, in a total of 35,445 patients discharged, alive or dead, the mortality ratio was 11 per cent; since then it has increased steadily until it was 19 per cent in 1936—the level reached, it is to be noted, by the New York and New Jersey institutions in recent years.

### INTRODUCTION OF COLLAPSE THERAPY

The part which surgical treatment of pulmonary tuberculosis has now come to take may be seen from the following: In 1932 in a survey made of all hospitals in New York City, and of certain neighboring institutions in New Jersey, the writer found that 19 per cent of patients in New York City hospitals were given some form of collapse therapy; in the New Jersey institutions, the proportion was already higher, 36 per cent.

The Council on Medical Education and Hospitals of the American Medical Association, in the survey, mentioned previously, of Tuberculosis Hospitals and Sanatoriums in the United States, reports in the chapter on special therapeutic measures that, based upon returns received during 1934 from 502 institutions with 74,083 beds, pneumothorax treatments were "initiated" in 16,401 patients; also, that there were performed in addition, though not necessarily always on new patients, 929 pneumolyses, 2,076 oleothoraces, 2,935 thoracoplasties, and 7,695 phrenic nerve operations.

Furthermore the application of collapse therapy is not confined to patients in sanatoria; the same survey of the American Medical Association disclosed that in the out-patient services of the institutions reporting in 1934 another 6,711 patients were under pneumothorax treatment. No figures are available as to the extent of its use in private medical practice, but its present popularity is high and this raises correspondingly the proportion of the tuberculous under specific treatment.

Cutler (4) of the Henry Phipps Institute, Philadelphia, writes, "During the past decade, pneumothorax therapy has been applied to an ever increasing number of tuberculous patients, so that many institutions report 75 per cent or more of their cases as receiving artificial pneumothorax treatment. This is in striking contrast to the usual 5 to 10 per cent of five or ten years ago."

Thus during the past few years we have witnessed on an ever widening scale the introduction of a new and deep-reaching, modifying factor in the treatment of tuberculosis, the effects of which should now become apparent upon case fatality rates in tuberculosis.

No more direct reference is made here to the possible results of sanatorium or surgical treatment because, as previously mentioned, a number of adequate and well conducted studies are already available. The general results of sanatorium treatment have been carefully studied on an actuarial basis for places like Trudeau, Frimley or Midhurst in England and reviewed again recently by Hilleboe (5, 6, 7, 8). With regard to artificial pneumothorax, excellent reports have been completed recently in England, for instance, by Bentley (9) with follow-up over a long period of years, of cases treated under the Anti-Tuberculosis Scheme of the London County Council. He concludes that only a small proportion of all patients undergoing residential treatment were considered suitable to receive it and that "the survival in all the cases investigated was approximately 20 per cent higher in the pneumothorax group than the expected number amongst those conservatively treated;" also, "that a 20 per cent improvement in 10 per cent of patients would heighten the general level of results in all cases undergoing residential treatment by 2 per cent" only; finally, that "the application of artificial pneumothorax cannot be expected . . . to alter materially the gross statistics of the results of antituberculosis schemes, but it will continue to be of vital importance to selected individual sufferers."

### RESULTS OF ARTIFICIAL-PNEUMOTHORAX TREATMENT

As against the comparatively favorable opinion of Bentley with regard to artificial pneumothorax there has come to hand more recently a still broader report presented to the Joint Tuberculosis Council on *The Results of Artificial Pneumothorax Treatment,* Brand *et al.* (10). These workers enlisted the help of Stockman, an actuary having experience in similar investigations. After a careful analysis of the survival rate of 3,021 cases of pulmonary tuberculosis treated in 42 different hospitals by artificial pneumothorax and followed up to the end of 1932, and of 1,329 cases in the same hospitals in whom attempts to induce artificial pneumothorax failed or were abandoned, the findings were compared with the results of sanatorium treatment in 2,750 cases treated at the King Edward VII Sanatorium, Midhurst (where less than one per cent were treated by artificial pneumothorax). They were unable to find any distinct advantage, or more favorable ratio of actual to expected deaths, among those treated over those not so treated. This careful investigation led the Lancet to remark editorially "It is impossible to avoid a feeling of disappointment . . . that painstaking and comprehensive work

should have failed to establish a statistical basis of the advantages of pneumothorax treatment."

### SEGREGATION OF TUBERCULOSIS CASES

While, therefore, there would seem to be little conclusive evidence that institutional or modern treatment has had any marked influence upon the community case fatality rates from tuberculosis, still it is obvious that by segregating an increasingly large proportion of open cases there are preventive values in institutional care which are in great part responsible, along with the improvement of living and environmental conditions, for the acknowledged decrease of tuberculosis. In table 12 is illustrated the growth of the sanatorium movement and the increasing proportion of tuberculosis cases segregated or "isolated" nowadays in institutions. In New York State, for instance, in 1915, according to surveys of the National Tuberculosis Association, there were 7,701 beds available in sanatoria and hospitals. It is possible, with the knowledge that there were 16,444 deaths from tuberculosis in the entire State during that year, to estimate quite closely the proportion "isolated." Thus, first allowing for an 85 per cent occupancy of the hospital beds, we have an average daily use, or segregation of cases, totalling 6,545 at that time. Practical experience permits us to estimate the existence in the community of an average of five frank cases of tuberculosis for each death. This would indicate in the State of New York in 1915 some 82,220 living cases and, as against the beds occupied, that 8 per cent of all tuberculosis cases, or one out of every twelve, were then "isolated." In 1925, the National Tuberculosis Association recorded in the State of New York 11,546 tuberculosis beds. With an occupancy of 90 per cent, or an average of 9,391 as a daily census, and 10,173 deaths that year, or roughly 50,865 living frank cases in the State, it would appear that 18 per cent or nearly one out of every five were then segregated or "isolated." In 1935, the same authority listed 13,989 beds; and with the deaths numbering 7,427 that year, it may be figured that probably out of 37,135 cases in the State there were 34 per cent "isolated," or one out of every three—a proportion four times as great as twenty years previously.

As detailed in table 12, for the United States as a whole, in 1915, we see only about 4 per cent of all the tuberculosis cases segregated. In 1934, when the survey by the American Medical Association uncovered a total of 93,531 beds, either in sanatoria or in tuberculosis departments of various hospitals, and there were 71,609 deaths, or roughly some 358,000

cases in the entire country, 25 per cent, or six times as many as previously, were "isolated." In England, reports at hand of "residential treatment" cover the years 1921, 1930 and 1934. In 1921, about 8 per

TABLE 12

*Approximate proportion of all tuberculosis cases "isolated" in hospitals and sanatoria—State of New York, United States and England*

| COMMUNITY | HOSPITAL BEDS | | TUBERCULOSIS | | PROPORTION OF ALL CASES HOSPITALIZED OR SEGREGATED |
|---|---|---|---|---|---|
| | Available | Occupied daily | Deaths in entire community | Total living cases (h) on a given date | |
| I. New York State: | | | | | |
| 1915 | 7,701 (a) | 85% = 6,545 | 16,444 (e) | 82,220 | 8% or 1/12 |
| 1925 | 11,546 (a) | 90% = 9,391 | 10,173 (e) | 50,865 | 18% or 1/5 |
| 1935 | 13,989 (a) | 90% = 12,590 | 7,427 (e) | 37,135 | 34% or 1/3 |
| II. United States: | | | | | |
| 1915 | 35,000 (b) | 85% = 29,750 | 145,000 (f) | 725,000 | 4% or 1/25 |
| 1926 | 67,270 (a) | 85% = 57,180 | 101,968 (f) | 509,840 | 11% or 1/9 |
| 1934 | 93,531 (c) | 90% = 84,180 | 71,609 (f) | 358,045 | 25% or 1/4 |
| III. England: | | | | | |
| 1921 | 18,943 (d) | 85% = 16,100 | 39,498 (g) | 197,490 | 8% or 1/12 |
| 1930 | 24,578 (d) | Jul. 1 = 21,153 | 33,178 (g) | 165,890 | 13% or 1/8 |
| 1934 | 27,369 (d) | Jul. 1 = 24,133 | 28,551 (g) | 142,750 | 17% or 1/6 |

(a) From annual issues of the Tuberculosis Sanatorium Directory, National Tuberculosis Association.

(b) Drolet (2), Tuberculosis Hospitalization.

(c) American Medical Association (3), Survey of Tuberculosis Hospitals and Sanatoriums.

(d) From annual reports, Chief Medical Officer, Ministry of Health, particularly sections dealing with "approved residential institutions."

(e) From reports, Division of Vital Statistics, Department of Health, State of New York.

(f) Based on Mortality Statistics, U. S. Bureau of the Census, and prior to 1934 on the assumption that the mortality rate in the Registration Area prevailed in the entire United States.

(g) From the reports of tuberculosis mortality in England and Wales there have been deducted the deaths in Wales and Monmouthshire noted in the reports of the King Edward VII Welsh National Memorial Association.

(h) Estimated by figuring that there are on an average five living frank or manifest cases of tuberculosis to each annual death as noted in the appraisal form of the American Public Health Association.

cent of all the tuberculosis cases may be said to have been "isolated" then; in 1915, the proportion was probably as low as that of the United States—around 5 per cent. In 1930, in England, those segregated had risen to 13 per cent or one out of every eight cases; in 1934, "residential

treatment in approved institutions" was being given to an average of nearly 25,000 cases, or 17 per cent of the probable total living frank cases of tuberculosis. Therefore, in England, the proportion of cases "isolated" is twice as large as in 1921 and probably four times that in 1915.

It may, therefore, be concluded from the obvious decline of tuberculosis and the comparatively slight change in the case fatality rate that the preventive aspects of isolation in tuberculosis hospitals have been far more effective than those arising from sanatorium or medical treatment.

## SUMMARY

1. The ratio of deaths to new cases of tuberculosis reported in various communities has varied little during the past twenty years: in New York City or in the remainder of the State, by 5 per cent; in New Jersey, in Massachusetts and in England and Wales, by only 1 or 2 per cent; in Detroit or Philadelphia, by 5 or 6 per cent; in Chicago, not at all——all the while that the incidence of the disease and the mortality were declining anywhere from 40 to 64 per cent.

2. The ratio of deaths to cases, after being comparatively high in young children under five years of age, from an ebb in the group five to fifteen years advances steadily with age.

3. Persons dying from tuberculosis now are, on an average, slightly older than formerly. In the United States, in 1913, males averaged at death 36.4 years, females 32.5; in 1933, they reached 41.5 years and 35.8 respectively. In England and Wales, in 1914, males averaged 32.6 years and females 29.0 years; in 1935, 38.9 years and 32.8 years respectively.

4. The mortality ratio to the total discharges, alive or dead, among sanatorium or hospital treated cases since 1910 in New York City has tended to become lower, being at first 29 per cent and, in 1917, 25 per cent. In institutions of the entire metropolitan area, it was still 25 per cent in 1927, but came down to 19 per cent in 1932 and rose slightly to 21 per cent in 1936. During the last decade chest surgery has come into increasing use, being now applied in the local institutions to possibly one-quarter or one-third of the cases. In the United States among patients in sanatoria in 1925, the mortality ratio was 20 per cent; in 1931, 23 per cent; and, in 1934, 24 per cent. In England, the mortality ratio in "approved residential institutions" was 11 per cent in 1927 and has risen steadily, being 19 per cent in 1936.

5. As compared with some time ago, the proportion of all tuberculosis

cases "isolated" in hospitals is several times greater now: in the State of New York, in 1935, one out of every three cases, or 34 per cent, is segregated in institutions and the proportion is four times that of twenty years ago when only one out of twelve was isolated, or 8 per cent of the total cases. In the United States, the proportion of all living cases "isolated" has risen from 4 per cent in 1915 to 25 per cent in 1934; and, in England, between 1921 and 1934, has doubled, passing from 8 per cent to 17 per cent.

6. Sanatorium or surgical treatment of pulmonary tuberculosis would seem so far to have had little effect upon the case fatality rates of the entire tuberculous population in the communities studied. Even with a continuing difficulty in securing the recovery of tuberculosis patients under sanatorium treatment, segregation of active cases, along with other general sanitary measures and the improvement of living and working conditions, has undoubtedly been a powerful factor limiting infection and preventing the spread of tuberculosis.

## REFERENCES

(1) FROST, W. H.: The epidemiology of tuberculosis as bearing upon its control, Thirteenth Fall Meeting, Eastern Section American Sanatorium Association, October 30, 1936, New York City.

(2) DROLET, G. J.: Tuberculosis hospitalization in the United States, Amer. Rev. Tuberc., 1926, *14*, 600.

(3) Amer. Med. Assn., Council on Medical Education and Hospitals: Survey of tuberculosis hospitals and sanatoriums in the United States, Jour. Amer. Med. Assn., 1935, *105*, no. 23.

(4) CUTLER, J.: The increasing importance of pneumothorax therapy in pulmonary tuberculosis, Ibid., 1936, *106*, 1366.

(5) ELDERTON, W. P., AND PERRY, S. J.: A fourth study of the statistics of pulmonary tuberculosis; the mortality of the tuberculous; sanatorium and tuberculin treatment. Based on Lawrason Brown's Adirondack Sanitarium data, Drapers' Research Memoirs, VIII, London, 1913.

(6) BARDSWELL, N. D., AND THOMPSON, J. H. R.: Pulmonary tuberculosis. Mortality after sanatorium treatment. A report of the experience of the King Edward VII Sanatorium, Midhurst, Medical Research Committee, Special Report No. 33, London, 1919.

(7) HARTLEY, P. H. S., WINGFIELD, R. C., AND THOMPSON, J. H. R.: An inquiry into the after-histories of patients treated at the Brompton Hospital Sanatorium, Frimley, Medical Research Council, Special Report No. 85, London, 1924.

(8) HILLEBOE, H. E.: The comparative mortality of patients discharged from tuberculosis sanatoria, Amer. Rev. Tuberc., 1936, *34*, 713.

(9) BENTLEY, F. J.: Artificial pneumothorax: experience of the London County Council, Medical Research Council, Special Report No. 215, London, 1936.

(10) BRAND, N., EDWARDS, P. W., HAWTHORNE, C. O., *et al.*: The results of artificial pneumothorax treatment: reports to the Joint Tuberculosis Council, Tubercle Supplement, February, 1937, London.

# SELECTIVE THORACOPLASTY WITH LUNG MOBILIZATION[1,2]

## The Conservative Goal in Permanent Collapse Therapy

RICHARD H. OVERHOLT

The number of far advanced cases of pulmonary tuberculosis to be rehabilitated by a permanent collapse of the diseased lung is increasing steadily. The principles underlying thoracoplasty are well understood and the advisability of obtaining cavity closure and sputum conversion is generally admitted. Recently there has been little hesitation in recommending thoracoplasty in the essentially unilateral case, if incapacitation is complete and other measures fail or would obviously be ineffectual in arresting the disease. When an empyema complicates a pneumothorax surgical aid is frequently called upon. There is considerable doubt in the minds of many, however, as to the advisability of subjecting patients, who do not fall into these two categories, to the discomforts and risks of thoracoplasty in order to close pulmonary cavities.

The argument is advanced that the patient with long-standing stationary disease, who has learned how to live with his tuberculosis, may be better off in the long run with the cavity open than with a deforming or disabling alteration of the thoracic wall. Brown and Sampson (1) have seriously questioned the place of thoracoplasty in the treatment of the "good chronic" patient. There is also the patient with bilateral cavitation or with continual fever and progressive disease in whom thoracoplasty has been thought to be contraindicated. Discouraging reports on late results from thoracoplasty have been made by Wiener and Fishberg (2) and by Matz (3).

It is true that the surgical treatment of tuberculosis has had to grow and progress with advances in thoracic surgical management. It is also apparent that we should not build up our concept of the value of thoracoplasty from results obtained from last-resort procedures, often

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Department of Thoracic Surgery, the Lahey Clinic, Boston, Massachusetts.

applied years too late in the course of the disease and carried out at a time when thoracic surgery was in its infancy. As the most ideal combined medical and surgical service is developed for those patients in need of permanent collapse therapy the results should improve and more serious risk patients be given the benefits of such treatment.

A sufficient number of patients have now had the advantage of being treated under more ideal conditions in various clinics for thoracic surgery to begin to evaluate results. A report on true late results will require more time. A fair evaluation of operative risk and of probable benefits can be made. It is highly important to know how far we can go with the patient with progressive or bilateral disease. The obligation of the surgeon not only rests with the rehabilitation of the good chronic but also with preventing an almost certain death from tuberculosis in the otherwise hopeless case.

During the five years the Department of Thoracic Surgery has been established in the Lahey Clinic (May, 1932 to May, 1937), 370 patients have been treated by thoracoplasty, with 763 operations. A description of the technique, upper selective thoracoplasty, used during the first half of this period has been given (4). The technique used during the past two and one-half years, thoracoplasty with lung mobilization, has also been published (5). A recent survey of the results in all patients has been made and the present status of the living cases has been ascertained. Several factors concerning this series of patients are of interest.

*1:* The group represents a consecutive series of patients operated by the same surgical team.[3]

*2:* All operations have been done during the period of the development of upper selective thoracoplasty. Every operation, except two, were of the above-down type with an extensive resection of the upper three ribs. Complete resections, more than 7 or 8 ribs, were avoided whenever possible.

*3:* Second or subsequent stages were carried out as delayed procedures. Practically all patients returned to their respective sanatoria after the first operation. Second or subsequent stages were not done unless there was positive sputum or X-ray evidence of a persisting cavity. In other words, clinical proof of the necessity for additional permanent collapse was required before each individual stage was undertaken. A period of six weeks or more usually elapsed between operations.

*4:* In more than half of the patients a mobilization of the upper lobe supple-

[3] All operations were done either by the author or by Dr. J. S. Harter who was on the Lahey Clinic Staff during 1935 and 1936.

mented the decostalization, that is, vertical collapse of the apex and forward mobilization of the lung in the vertebral gutter.
*5:* An increasingly higher percentage of poor risk cases were accepted for thoracoplasty year by year, including progressive and febrile patients and those having bilateral cavitation.

## PREOPERATIVE CLASSIFICATION

The great variation in the types of patients accepted for thoracoplasty lead us to adopt the following classification.

*Group 1:* Patients having an essentially unilateral disease, however extensive on one side, in the stationary phase, the so-called "good chronic" unilateral case. The larger majority were receiving treatment in sanatoria and were incapacitated but their life was not immediately endangered by the disease. (See figure 1.)
*Group 2:* Patients having bilateral involvement with the better lung in a quiescent state and without roentgenological evidence of an open cavity in the better lung. These patients have also been considered "good chronics" and fair risks for thoracoplasty. (See figure 2.)
*Group 3:* Patients with bilateral involvement with open cavities in the contralateral lung, or the contralateral lung controlled by pneumothorax, thoracoplasty, or plombage. Heretofore, these patients were considered unsuitable for permanent collapse therapy because of the extent and distribution of the disease. Possibilities of extension in the contralateral lung and discouraging later results were feared. The operation was advised as a life saving measure. (See figures 3, 4 & 6.)
*Group 4:* Patients having complications serious enough to make them poor risks from the point of view of operative mortality or late results. In this group, as well as in group 3, surgery presented the only alternative. A subdivision of group 4 has been made and illustrates the type of patient falling in this classification:

(*1*) A patient with a progressive lesion by X-ray, extending in the face of absolute bed-rest and other measures failing or obviously ineffectual.
(*2*) Tuberculous or mixed empyema complicating pulmonary tuberculosis. (See figure 5.)
(*3*) Extrapulmonary tuberculosis or other complications of sufficient severity to increase definitely the operative risk or influence the late result. (Intestinal tuberculosis, amyloid disease, severe laryngeal tuberculosis or tracheal ulceration, renal tuberculosis, etc.)

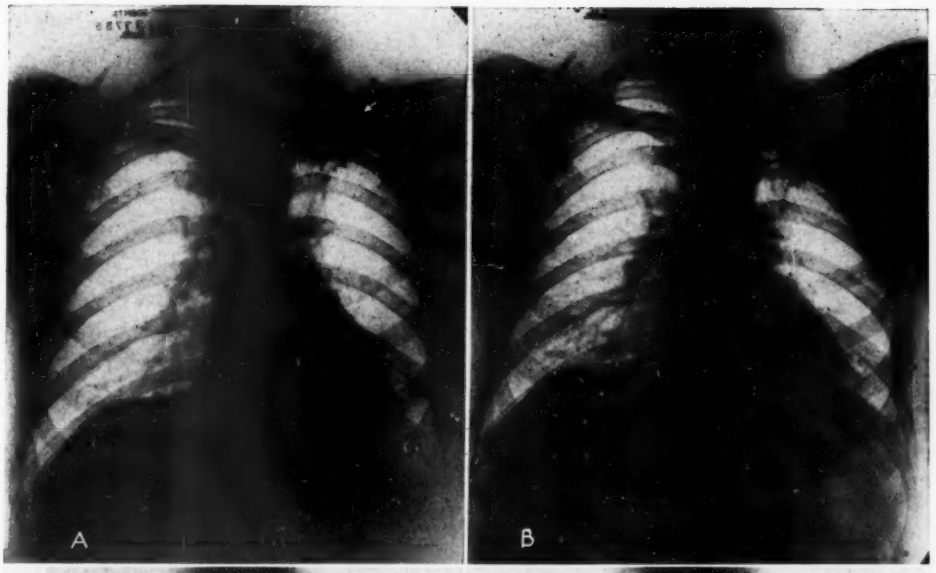



FIG. 1A

FIG. 1B

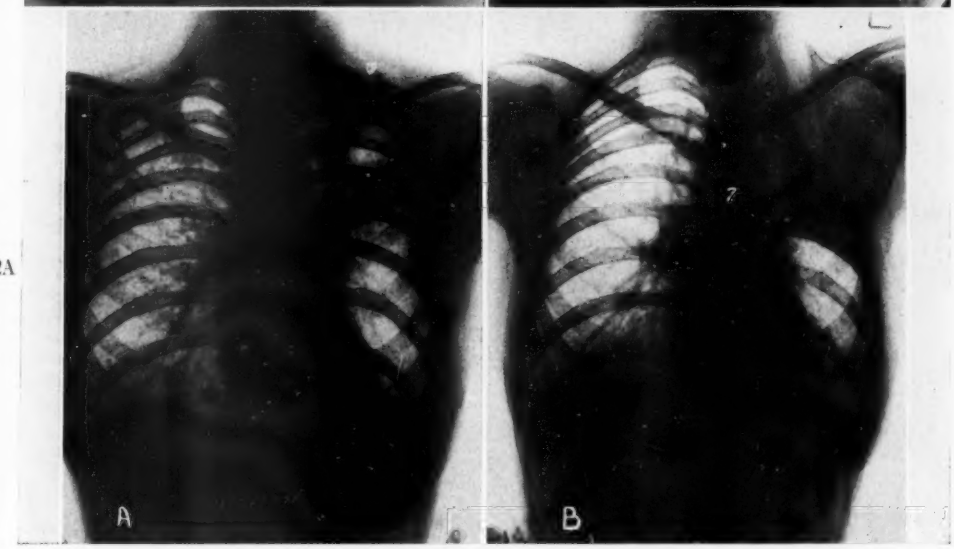



FIG. 2A

FIG. 2B

FIG. 1. Mr. G. B., age 25 years. A. Group 1, essentially unilateral, "good chronic." Nine-year history with recent haemoptysis. B. Roentgenogram seven months after 3-rib thoracoplasty with mobilization of upper lobe. Consistently negative sputum, freedom of symptoms and disappearance of cavities after single operation. Note effectiveness of collapse and noninterference with uninvolved lung.

FIG. 2. Miss M. D., age 30 years. A. Group 2, bilateral involvement with better lung quiescent. Duration of disease two and one-half years. Left, partial pneumothorax maintained four months. Note larger cavity in left lung and fibrosis in the right lung. B. Roentgenogram two months after 7-rib thoracoplasty with mobilization of the left upper lobe. Note adequacy of collapse and expanded lower lobe. This form of selective and permanent collapse was the most conservative treatment possible for such an extensive area of cavitation. The patient now is without symptoms, is home and working and has no dyspnoea on moderate exertion.

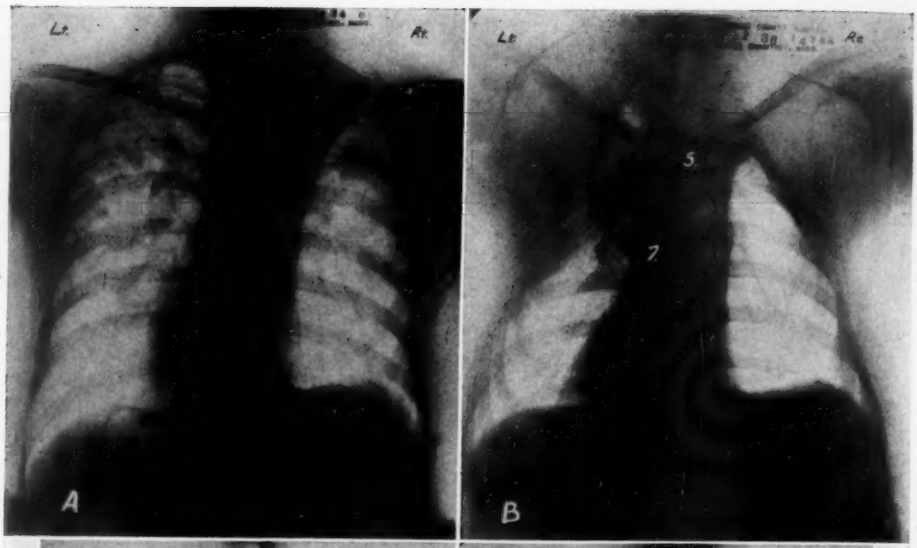



FIG. 3A

FIG. 3B

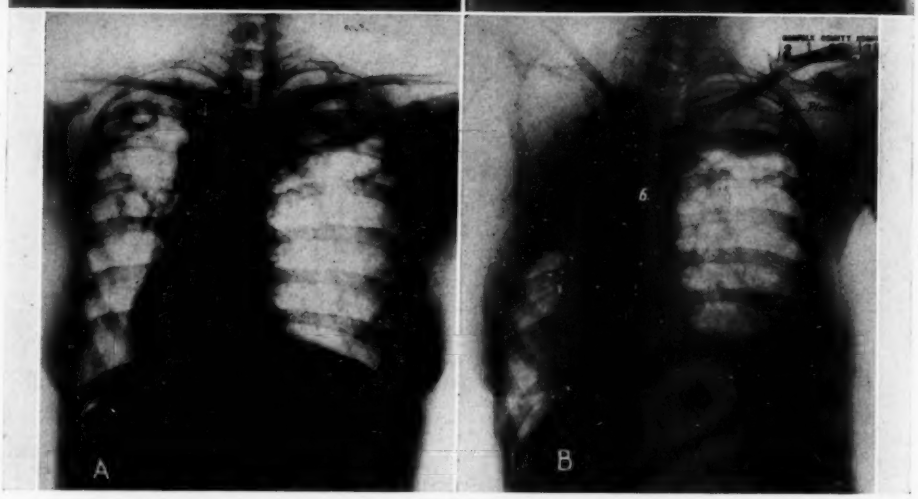



FIG. 4A

FIG. 4B

FIG. 3. Mr. W. H., age 32 years. A. Group 3, bilateral disease with cavitation in both upper lobes of two years' duration. Note extensive disease with mediastinum and trachea displaced to the right. Pneumothorax unsuccessful on either side. Phrenic paralysis contraindicated because of active bilateral disease and necessity for apical collapse. B. Roentgenogram five months after last operation of four stages, 5 ribs on the right, 6 ribs on the left. Selective apical collapse is essential in bilateral disease. Patient is now classified as apparently arrested and is without symptoms except for slight dyspnoea on exertion.

FIG. 4. Mrs. L. Q., age 47 years. A. Group 3, bilateral cavitation with symptoms for seventeen years and sanatorium treatment for three years. Note contraction of heavily fibrosed upper lobes and distortion of the hilar shadow. Pneumothorax unsuccessful on either side. B. Roentgenogram taken sixteen months after last operation. Left plombage June, 1935, with incomplete closure of cavities. Right plombage August, 1935, with closure of cavities. Left first-stage thoracoplasty in November, 1935, with removal of paraffin. Second-stage thoracoplasty January, 1936 (three months later). Note effectiveness of cavity closure and conservation of lower lobes. Patient is now home with her family and enjoying ordinary activities of life.

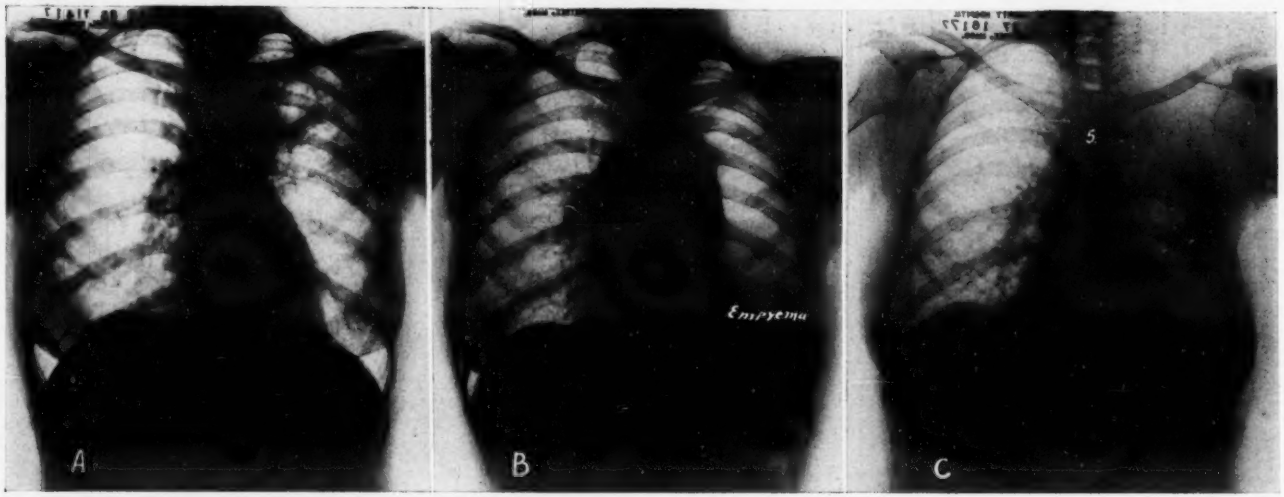



FIG. 5. Miss L. L., age 47 years. A. Group 4, extensive involvement left upper lobe. Duration of disease three years, hospitalized 15 months. B. After pneumothorax complicated by tuberculous empyema. Note extent of collapse and sacrifice of lower lobe. C. Six months after upper selective thoracoplasty, two stages, 5 ribs, with long period between. Lower lobe permitted to reëxpand; this treatment was the most conservative form of collapse for this patient. She is now perfectly well, is home, and has no dyspnoea on exertion.

## PATIENTS INCLUDED IN STUDY

A general summary of cases treated in the five-year period, May, 1932 to May, 1937, is shown in table 1. It is obvious that an accurate ap-

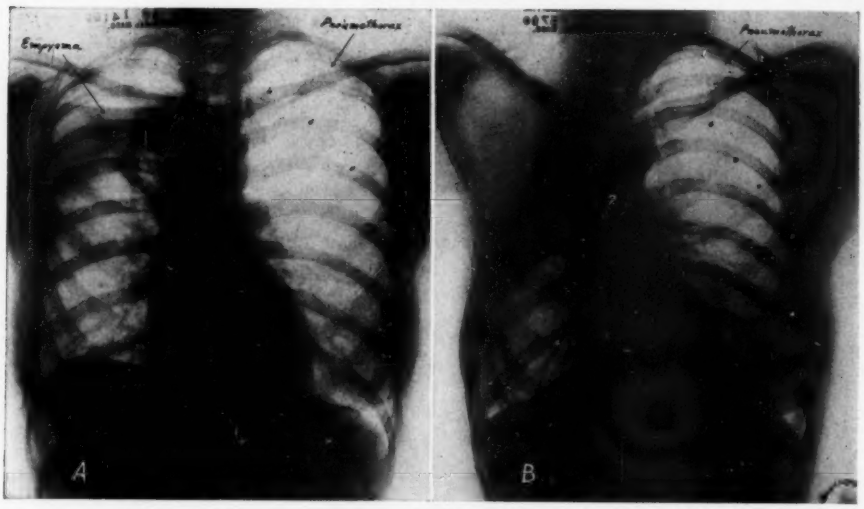



FIG. 6. Miss E. O'J., age 21 years. A. Groups 3 and 4, bilateral involvement with satisfactory partial pneumothorax on the left side and a tuberculous empyema on the right side. Duration of disease two years. B. Roentgenogram taken five months after right upper thoracoplasty (two stages, 7 ribs) with mobilization of the upper lobe. Cavities are closed and sputum is consistently negative. Note conservative type of thoracoplasty.

TABLE 1*

*Thoracoplasty survey—five year period, May, 1932 to May, 1937*

| | |
|---|---|
| Total number patients | 370 |
| Number of operative stages | 763 |
| Operative deaths | 20 |
| Patient mortality | 5.4% |
| Mortality per operation | 2.6% |
| Late sanatorium deaths (15 tuberculous; 6 deaths nontuberculous) | 21 |
| Abandonment further stages | 4 |
| Recent or unfinished cases | 63 |
| Discharged against advice | 8 |
| Total living cases—thoracoplasty considered complete | 254 |

* Table showing total number of patients treated. Every case of pulmonary tuberculosis treated by thoracoplasty by the author has been included to compute mortality figures. Patients operated within the past six months were not used in the evaluation of results.

praisement of late results cannot be made on patients operated within the past two years. The immediate operative risk can be shown. It is important to know what is happening to the operative mortality as more

serious risks are accepted. The routine use of the supplementary procedure of lung mobilization carried out at the time of thoracoplasty also should be evaluated in the light of possible added operative risk.

TABLE 2*

*Classification of patients accepted for thoracoplasty*

| | THORACOPLASTY | THORACOPLASTY AND MOBILIZATION | TOTALS | |
|---|---|---|---|---|
| Group 1 | 25 | 34 | 59 | 206 good chronics |
| Group 2 | 55 | 92 | 147 | |
| Group 3 | 21 | 52 | 73 | 164 poor risks |
| Group 4 | 24 | 44 | 68 | |
| Groups 3 & 4 | 13 | 10 | 23 | |
| Totals | 138 | 232 | 370 | |

* Table showing type of patient accepted for thoracoplasty with separate listing for those having upper selective thoracoplasty alone or with lung mobilization.

Group 1. Unilateral, stationary.

Group 2. Bilateral, better lung quiescent without X-ray evidence of cavity.

Group 3. Bilateral cavitation, better lung with open cavities, pneumothorax, plombage or bilateral thoracoplasty.

Group 4. Complicated cases: (a) febrile, progressive forms—28 patients; (b) tuberculous or mixed empyema—32 patients; (c) extrapulmonary complications—31 patients.

TABLE 3

*Deaths*

| | OPERATIVE DEATHS | | LATE SANATORIUM DEATHS | |
|---|---|---|---|---|
| | Thoracoplasty | Thoracoplasty and mobilization | Thoracoplasty | Thoracoplasty and mobilization |
| Group 1 | 0 | 2 | 1 | 0 |
| Group 2 | 4 | 1 | 3 | 2 |
| Group 3 | 2 | 5 | 3 | 1 |
| Group 4 | 2 | 0 | 3 | 4 |
| Groups 3 & 4 | 1 | 3 | 2 | 2 |
| Totals | 9 | 11 | 12 | 9 |
| Percentages | 6.5 | 4.7 | 8.7 | 3.8 |

The entire group of 370 patients has been used to indicate the type of patients accepted for thoracoplasty (table 2). In determining percentages in the tables of operative and late deaths (tables 3 & 4) the total number of patients treated was used. In averaging the number

of stages and extent of the thoracoplasty carried out only the apparently completed cases were used. In table 1 there is indicated the number of patients, 116, that obviously should not be included, leaving 254 patients

TABLE 4

*Deaths in relation to good and poor risk groups*

| | NUMBER OF PATIENTS | OPERATIVE DEATHS | | LATE DEATHS | |
|---|---|---|---|---|---|
| | | Number | Per cent | Number | Per cent |
| Groups 1 & 2 | 206 | 7 | 3.4 | 6 | 2.9 |
| Groups 3 & 4 | 164 | 13 | 7.9 | 15 | 9.1 |
| Totals | 370 | 20 | 5.4 | 21* | 5.6 |

* Six of the deaths recorded as late or sanatorium deaths were due to causes not related to pulmonary tuberculosis. If the figures were corrected for this, the number of patients would be 15, and the percentage 4 instead of 5.6.

TABLE 5

*Extent of thoracoplasty*

| | THORACOPLASTY | THORACOPLASTY AND MOBILIZATION | ALL PATIENTS |
|---|---|---|---|
| Average number of stages | 2.4 | 2 | 2.2 |
| Average number of ribs | 7.1 | 6.5 | 6.7 |

TABLE 6

*Proportion of partial to complete thoracoplasty (254 patients—259 thoracoplasties—4 bilateral)*

| | THORACOPLASTY | | THORACOPLASTY AND MOBILIZATION | |
|---|---|---|---|---|
| | Number | Per cent | Number | Per cent |
| Total thoracoplasties | 112 | | 147 | |
| One-stage | 21 | 19 | 36 | 25 |
| 5 ribs or less | 23 | 20 | 39 | 26 |
| 8 ribs or less | 64 | 57 | 96 | 66 |
| Complete | 25 | 22 | 12 | 8 |
| Anterolateral | 20 | 18 | 1 | 0.7 |
| Revisions | 24 | 21.4 | 3 | 2 |

for the analysis shown in tables 5, 6 & 7. In table 8 an evaluation of the condition of "good chronic" and "poor risk" group has been made as to the benefits of thoracoplasty. In such a study the deaths and

abandoned cases should be included in order to work out the percentages of cases actually helped by surgery. The 63 recent cases were eliminated.

TABLE 7*

*Present status 254 patients operated 1932–1936*

| | GROUP 1 | | GROUP 2 | | GROUP 3 | | GROUP 4 | | GROUPS 3 & 4 | | TOTALS | | ALL CASES |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T† | M‡ | T | M | T | M | T | M | T | M | T | M | |
| Worse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Same | 0 | 0 | 2 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 3 | 3 | 6 |
| Improved | 2 | 4 | 1 | 14 | 1 | 6 | 3 | 8 | 2 | 1 | 9 | 33 | 42 |
| Quiescent | 0 | 0 | 2 | 8 | 1 | 9 | 0 | 5 | 0 | 2 | 3 | 24 | 27 |
| Apparently arrested | 1 | 9 | 8 | 17 | 4 | 6 | 3 | 7 | 3 | 0 | 19 | 39 | 58 |
| Working | 21 | 8 | 34 | 25 | 8 | 5 | 11 | 7 | 2 | 0 | 76 | 45 | 121 |

* Living completed patients listed to show present condition in relation to preoperative classification.

† T = Thoracoplasty alone.

‡ M = Thoracoplasty plus lung mobilization.

In the bilateral cases, group 3, 16 patients had a contralateral pneumothorax, 4 a bilateral thoracoplasty and 2 a contralateral plombage.

TABLE 8

*Evaluation of condition in relation to good and poor risk groups*

| STATUS | GROUPS 1 & 2 | | GROUPS 3 & 4 | | BOTH GROUPS | |
|---|---|---|---|---|---|---|
| | Number | Per cent | Number | Per cent | Number | Per cent |
| Operative or late death | 13 | 7.5 | 28 | 20.7 | 41 | 13.38 |
| Same or operation abandoned | 4 | 2.3 | 6 | 4.4 | 10 | 3.2 |
| Discharged against advice | 1 | 0.5 | 7 | 5.2 | 8 | 2.6 |
| Totals not benefited | 18 | 10.5 | 41 | 30.6 | 59 | 19.2 |
| Improved | 21 | 12 | 21 | 15.5 | 42 | 13.68 |
| Quiescent | 10 | 5.8 | 17 | 12.5 | 27 | 8.8 |
| Apparently arrested | 35 | 20 | 23 | 17 | 58 | 18.8 |
| Working | 88 | 51.5 | 33 | 24.4 | 121 | 39.4 |
| Totals benefited | 154 | 89.5 | 94 | 69.4 | 248 | 80.8 |

In table 2 the types of cases accepted for thoracoplasty are shown. An explanation of the various groups has been given. For those patients falling into both group 3 and group 4, a separate listing is made. For example, a patient with bilateral cavitation (group 3) may also have an

empyema on one side (group 4) and in that event would be placed in a fifth classification, that of a combined 3 and 4 group. (See figure 6.) The operation was done without mobilization in 138 and with mobilization in 232. The great majority of the first group were done in the earlier years of the five-year period, 1932, 1933 and 1934, and those having mobilization were all done in the last two and one-half years, 1934, 1935 and 1936. The number of bilateral cases accepted for thoracoplasty has risen from 21 in the first period to 52 in the second. There are almost twice as many group 4 cases appearing in the mobilization group although many of the patients in group 4 had empyema and a mobilization could not be done. It is apparent from a study of table 2 that more serious risks are accepted for thoracoplasty from year to year.

There is indicated in table 2 the total number of good risk or favorable cases (206) and the number of unfavorable or poor risk cases (164). Groups 1 and 2 represent those patients who had a stationary process and so located in the lung that chances for success in surgical collapse of the diseased lung were good. It might also be considered that this group probably would have lived on for an indefinite period with their disease, provided they remained in the sanatoria with bed-rest and adequate supervision. Rehabilitation was the primary object of surgery.

The group 3, group 4 and combinations of 3 and 4 were all patients who were losing their fight against the disease and, even under the best care, would most likely succumb to the disease within the next few months or years. These patients were given the benefit of surgery primarily as a life-saving measure, with a hope that a certain proportion could be rehabilitated so that they might enjoy life with varying degrees of physical limitation. By so dividing all cases into these two general groups we find that 55 per cent can be considered good chronics, whereas 45 per cent were poor risk cases for thoracoplasty.

## DEATHS

In the entire series there were 20 operative deaths within the first three months following operation. Nine patients (6.5 per cent) died following operation, when mobilization was not done, and eleven patients (4.7 per cent) when mobilization was carried out. With added experience, increase in surgical skill, and improvement in postoperative management the operative mortality should steadily drop, providing there is no variation in the type of case selected. Justice is not being done to the poor risk and seriously ill patient if he is rejected in order to protect

one's mortality figures. It has been gratifying to know that it is possible to accept many bilateral and progressive cases, check extension of the disease by a first-stage thoracoplasty and mobilization of the upper lobe, and then after a period of several weeks continue on with subsequent stages and finally arrest the disease. We have also been gratified to learn that the addition of lung mobilization to the upper selective thoracoplasty has not increased the risk of operation.

There were 2 deaths in group 1 patients who also had lung mobilization. One of them was due to a pulmonary embolus occurring on the 14th day after a normal convalescence; the other was due to the development of severe paradoxical breathing after the second stage in a girl of 20 years of age. All efforts to combat the disorganized thoracic excursion failed. We are certain that a number of the deaths in the earlier cases in both groups could have been avoided with the use of methods employed at present.

Table 3 also indicates the number of late or sanatoria deaths among the thoracoplasty population. There is a higher percentage in the first series but this is to be expected because it is an older group, the great majority having been operated two and one-half years or more ago. It is significant that there have been so few deaths in the second period regardless of the fact that so many bilateral and progressive cases were included. The relation of the number of deaths to the good and poor risk groups is shown in table 4.

### THE EXTENT OF THE SURGICAL PROCEDURE

In evaluating the extent of the thoracoplasty necessary to arrest the process in the various types of patients accepted for operation 254 cases were analyzed, namely, those who are now considered to be completed. (See table 1.)

In table 5 the average number of stages and the average number of ribs resected are shown. It is interesting to note that most patients require only two operations and a seven-rib upper thoracoplasty. Those having the thoracoplasty supplemented by lung mobilization had fewer stages and slightly less number of ribs resected on the average. The two groups are hardly comparable, however, as more bilateral and extensive cases were included in the second group.

In table 6 the proportion of partial or upper selective thoracoplasties to complete operations is shown. In the mobilization group twice as many patients had 5 ribs or less, and 92 per cent had 8 ribs or less re-

sected. The most striking revelation in this comparison is the reduction in the number of revisions and in anterolateral operations. *Our experience seems to indicate that patients need be subjected to a less extensive decostalization if the upper lobe is mobilized at the time of the first stage.*

The present status of the completed and living cases is shown in table 7. The various cases are grouped according to their preoperative classification and as to lung mobilization. A fair comparison of the two groups can hardly be made in view of the fact that most of the patients having thoracoplasty without mobilization were done between five and two and one-half years ago, whereas the mobilization group were operated within the past two and one-half years. As time goes on many in the improved and quiescent group will move up into the apparently arrested class and many in the latter group will, in turn, be discharged and able to work.

In table 8 the good and fair risk cases, groups 1 and 2, have been combined and poor risk patients, groups 3 and 4, have been assembled for correlation as to the final result. In this table all cases have been included except the 63 recent cases. The table has been arranged to show the totals of all cases not benefited and those benefited by the operation. It is interesting to note that in the good chronic group 89.5 per cent were definitely helped, that 51.5 per cent have returned to work and that after a longer period of time the percentage will probably rise to 75 per cent. This estimation is arrived at by including those patients known now to be quiescent or apparently arrested. The complete rehabilitation of 75 per cent may even be exceeded as some of the improved group may in time move up into the other classifications.

With bilateral or progressive disease and in those patients with complicating factors the percentage of cases benefited has been found to be 69.4 per cent, with already 24.4 per cent back at work or completely rehabilitated.

The present status of the "good chronic" and poor risk groups is graphically illustrated in figure 7. A comparative summary of results of sanatorium treatment alone and of such treatment combined with thoracoplasty is shown in figure 8. Langmuir, Williams and Pope (6) made a study of the condition of a group of 506 patients five years after their admission to the Rutland State Sanatorium. Selected cases having an average of 12 months sanatorium treatment were used. The patients were admitted during the years of 1925 and 1926 and their status in 1930 and 1931 determined. Of those selected for the analysis, 208 were

classified as far advanced. The condition of the patients was reported as to their being dead, ill or well. The percentages from this report are shown in A of figure 6. Graph B of the same figure represents the composite study of all cases included in the present study. The percentages were taken from table 8. The comparison of the status of the

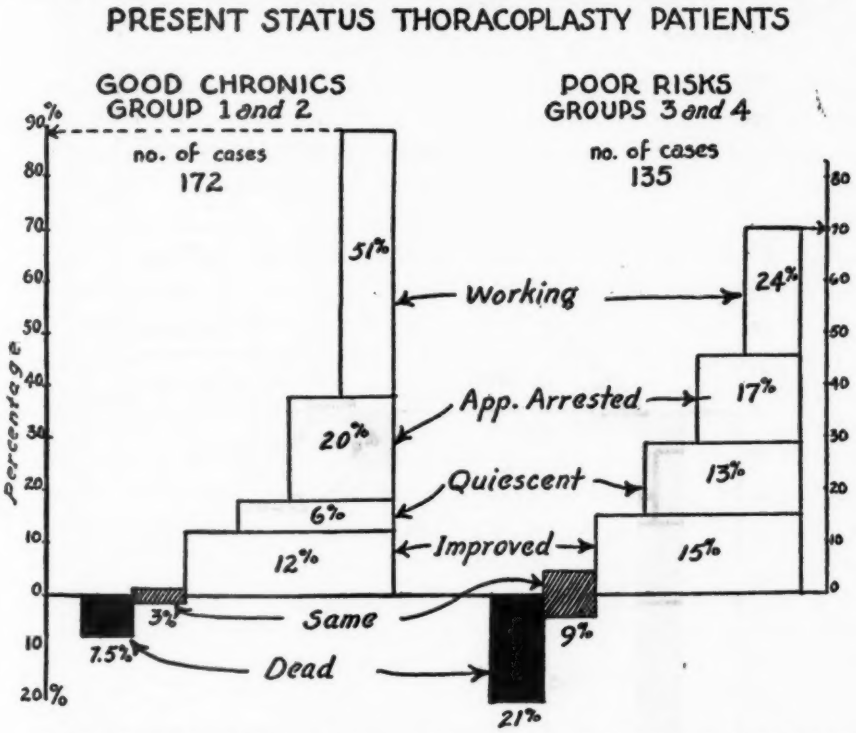



FIG. 7. Graph showing present status of 307 patients treated by thoracoplasty divided into "good chronics" (172) and "poor risks" (135). Figures are shown in percentages. See table 8. As time goes on many of the patients in the lower classes move up into the apparently arrested and working class. It is interesting to note that 89.5 per cent of the "good chronics" were improved by the operation and 69.4 per cent of the "poor risks" are known to be definitely improved.

patients in the two studies is interesting as it indicates the outlook for the far advanced patient now as compared to ten years ago. It should be pointed out, however, that the earlier study was made at the end of a five-year period and the thoracoplasty study was made on patients treated during a five-year period. It should also be pointed out that the thoracoplasty series consisted of practically all far advanced cases and

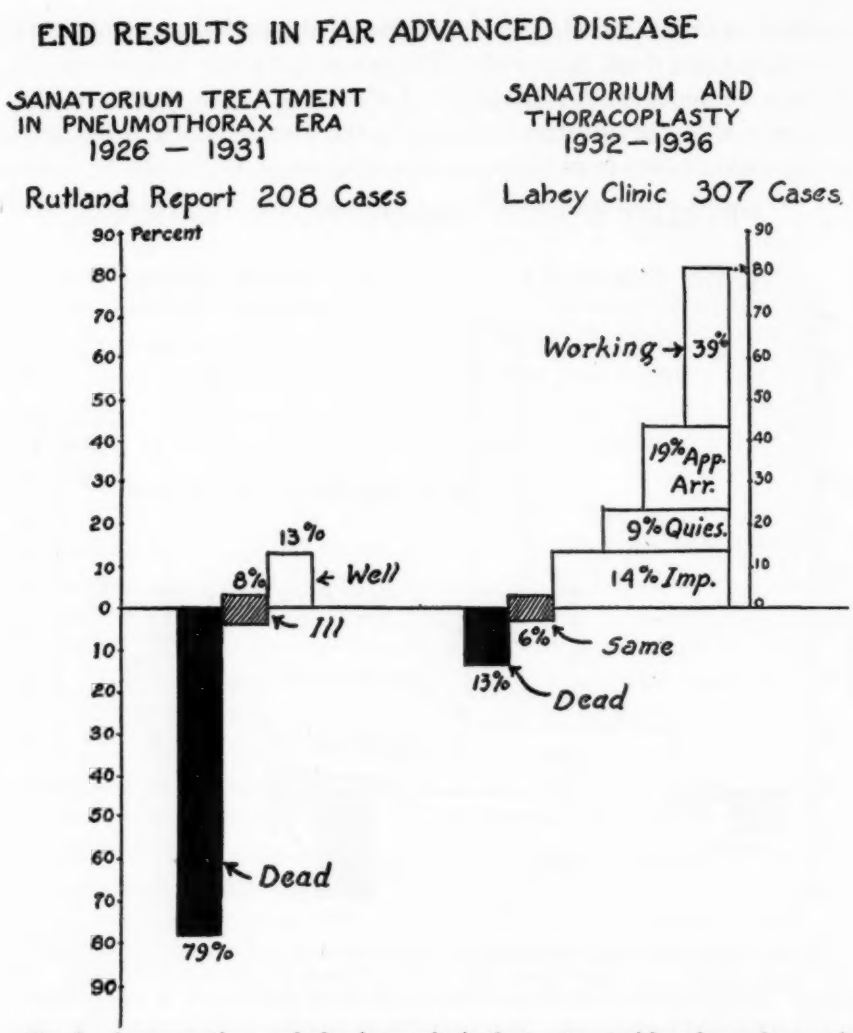



FIG. 8. A comparative graph showing results in the treatment of far advanced cases of pulmonary tuberculosis. From a reports of Langmuir, Williams and Pope (6) on five-year end results in selected patients admitted to Rutland State Sanatorium in the years 1925 and 1926. The authors of the Rutland report attempted to evaluate the effectiveness of sanatorium treatment. Cases falling in the following categories were excluded: (*1*) all patients under 17 years of age; (*2*) if residence was less than one month in the sanatorium; (*3*) if the disease had been present more than three years prior to admission; (*4*) all cases who died within three months of admission. Pneumothorax therapy was being used during the time these patients were being treated at the Rutland Sanatorium. The report emphasizes again the eventual high mortality in far advanced pulmonary tuberculosis. (b) Composite graph of present status of patients treated by thoracoplasty. Practically all subjects were in the far advanced stages of the disease. The value of an active program for permanent collapse therapy in far advanced disease is clearly shown.

the majority had already been resident in a sanatorium from one to five years before the operation was done.

### SPUTUM EXAMINATIONS

A report on the studies of the sputum in this series of postoperative patients is shown in figures 9 & 10. For this analysis the report of the medical staff of the sanatorium referring the patient was accepted. Repeated examinations after concentration were done in most instances and guinea-pig inoculation in a few. In figure 9 is shown the tabulation of the sputum in the various preoperative groups for the cases done without (T) and with (M) mobilization. The two groups are hardly comparable because of the difference in the periods the patients were treated and the difference in types. In the older group the patients were "worked over" until every possible surgical means to collapse cavities was exhausted. A great many had posterior revisions and anterolateral operations (table 6). The end results are good in those not having lung mobilization but the operations were more extensive and less conservative of the lower lobe. It will be noted that the patients having lung mobilization had a higher percentage of sputum conversion in the poor risk group. We have been greatly impressed by the number of patients who turn negative after the first stage providing the apex is mobilized. This provides a great factor of safety as subsequent operations are thereby undergone with less likelihood of an extension or a contralateral spread of the disease. Practically every patient had a positive sputum preoperatively. A few of the empyema cases who had turned negative as a result of previous pneumothorax treatment were negative at the time of their first-stage thoracoplasty. For practical purposes tables 9 and 10 indicate the effectiveness of thoracoplasty in converting a positive to a negative sputum.

### TUBERCULOUS OR MIXED EMPYEMA

The previous tables have included all cases of empyema complicating the pulmonary lesion. In table 11 is summarized data concerning 32 cases of tuberculous or mixed empyema which were included in the reports on group 4 patients. All cases were treated by repeated aspiration whenever possible. We considered it advisable to provide external catheter drainage in 6 patients. There was one operative death and there has been but one late death. The chest-wall is now closed in 28 patients and a sinus persists in 2 patients. Half of the living patients

FIG. 9

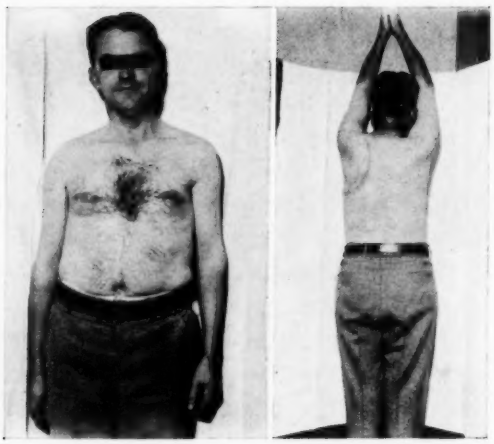


FIG. 10

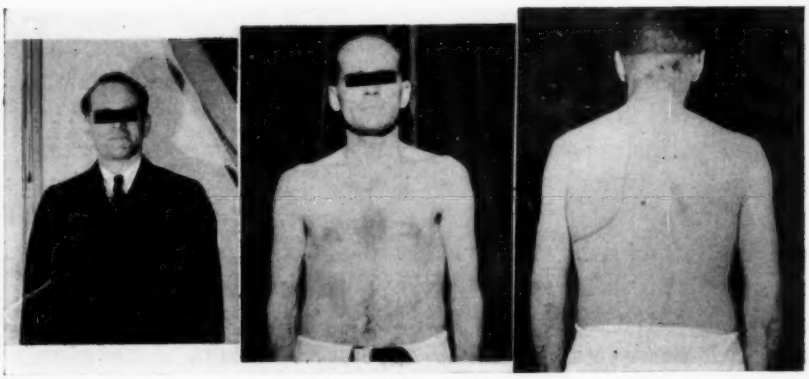


PLATE 1

FIG. 9. Mr. M. LeB., age 35 years. Left upper 7-rib two-stage thoracoplasty in January, 1935, provided adequate collapse of the left upper lobe. Has slight scoliosis with excellent shoulder function.

FIG. 10. Mr. Ed. K., age 38 years. Left upper 7-rib two-stage thoracoplasty in December, 1935. Complete rehabilitation without deformity.

have been discharged from their respective sanatoria and are able to work.

TABLE 9*

*Sputum examinations after operation in relation to preoperative classification*

| | GROUP 1 | | GROUP 2 | | GROUP 3 | | GROUP 4 | | GROUPS 3 & 4 | | TOTALS | | ALL CASES |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T | M | T | M | T | M | T | M | T | M | T | M | |
| Sputum positive..... | 1 | 1 | 3 | 8 | 2 | 3 | 3 | 3 | 3 | 0 | 12 | 15 | 27 |
| Sputum negative..... | 23 | 20 | 44 | 58 | 12 | 24 | 14 | 24 | 5 | 3 | 98 | 129 | 227 |

* Table showing results of recent sputum examinations in thoracoplasty subjects.
T = Thoracoplasty alone.
M = Thoracoplasty with lung mobilization.

TABLE 10

*Sputum examinations after operations in relation to good and poor risk groups*

| | GROUPS 1 & 2 | | | | GROUPS 3 & 4 | | | | ALL CASES | |
|---|---|---|---|---|---|---|---|---|---|---|
| | T | Per cent | M | Per cent | T | Per cent | M | Per cent | Number | Per cent |
| Sputum positive..... | 4 | 6 | 9 | 11 | 8 | 21 | 6 | 11 | 27 | 10.6 |
| Sputum negative..... | 67 | 94 | 78 | 89 | 31 | 79 | 51 | 89 | 227 | 89.4 |

TABLE 11*

*Tuberculous and mixed empyema complicating pulmonary tuberculosis (group 4 subgroup 2)*

| | |
|---|---|
| Total number..... | 32 |
| Operative deaths..... | 1 (3.1%) |
| Late deaths..... | 1 |
| Thoracoplasty + external drainage..... | 6 |
| Thoracoplasty + repeated aspiration..... | 26 |
| Chest-wall now closed..... | 28 |
| Persisting thoracic sinus..... | 2 |
| Thoracoplasty incomplete..... | 1 |
| Improved or quiescent..... | 14 |
| Discharged and working..... | 15 |

* Composite table summarizing results in the treatment of tuberculous or mixed empyema. These patients were included in the previous tables under the classification of group 4.

Our experience with tuberculous or mixed empyema has led us to believe that obliteration of the pleural space is the treatment of choice, avoiding if possible external drainage. In some a preliminary steriliza-

tion, or an attempt at sterilization, of the pleural cavity by oleothorax was carried out. In others we have proceeded with thoracoplasty without such treatment. The pleural fluid is withdrawn as the chest-wall is let down. The operation is done in carefully planned, delayed stages and in many instances where the original pulmonary disease did not involve the lower lobe there has been a partial reëxpansion of that lobe after an upper selective thoracoplasty (figure 5). All will agree that conservation of uninvolved pulmonary tissue is most desirable. Many times it has been regretted that a patient has had to forfeit an entire lung in order to collapse cavities in the upper lobe when a pneumothorax becomes complicated with a tuberculous empyema. The use of oleothorax is frequently not the most selective type of semipermanent collapse and, when used, may preclude the hope of reëxpansion. A permanent and adequate form of collapse of the upper lobe and an attempt at reëxpansion of the base is a step toward the conservative goal in collapse therapy.

## DISCUSSION

Destruction of considerable pulmonary tissue by a tuberculous process frequently leaves the patient with cavitation that does not close in spontaneously. There may be a failure of temporary forms of collapse therapy to effect cavity closure. A condition actually exists in which there is a discrepancy between the size of the healthy lung and the size of the thoracic cage. The spaces or cavities in the lung represent the difference in volume of the remaining lung and the volume of the thorax. A carefully planned and executed thoracoplasty readjusts the size of the thorax to correspond to the volume of the lung. When this is done selectively there is less interference with the function of healthy portions of the lung. Our experience indicates that the most selective and the most conservative thoracoplasty is one that is supplemented by lung mobilization. The type of collapse of the upper lobe thereby provided more nearly simulates a perfect upper selective pneumothorax than any form of permanent collapse yet devised.

Greater selectivity in collapse therapy makes it possible to accept for operation certain patients with bilateral disease. (See figure 12.) The areas of cavitation must be so distributed that it is technically possible to collapse them and still leave the patient with a fair pulmonary reserve. The collapse of the two upper lobes should not be much more expensive as to healthy pulmonary tissue than the collapse of two or

FIG. 11

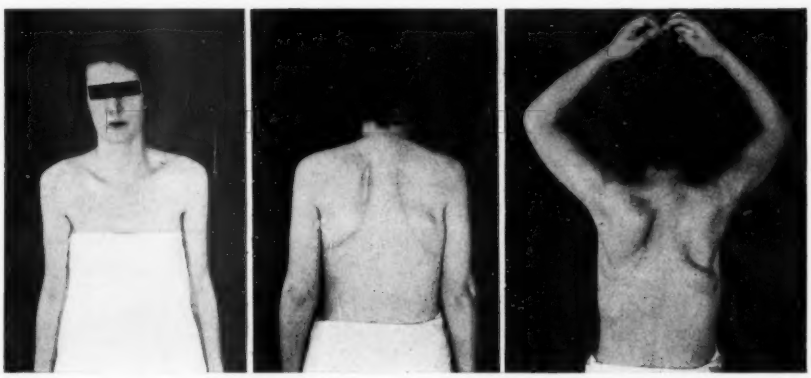


FIG. 12

PLATE 2

FIG. 11. Miss B. C., age 54 years. Dyspnoea and tightness in the chest were prominent preoperative symptoms. An old tuberculous process at the left apex had caused marked displacement of the mediastinum. trachea and heart to that side and there was elevation of the diaphragm. Following an upper selective thoracoplasty and mobilization of the upper lobe all symptoms disappeared, including the dyspnoea. The patient was completely rehabilitated.

FIG. 12. Miss E. M., age 26 years. Both upper lobes destroyed by disease of five years' duration. Last operation of a bilateral thoracoplasty in September, 1936. Disease apparently arrested and patient is now home and symptom free.

three lobes on the same side. The remaining lobes must be able to function. Therefore, in bilateral disease, phrenic nerve paralysis not only becomes of questionable value, but may be definitely contraindicated.

An inadequate pneumothorax or oleothorax which fails to control the pulmonary lesion and at the same time prevents expansion and function of an uninvolved lower lobe, may be a radical and wasteful type of collapse. For such patients an abandonment of the pneumothorax or oleothorax and the substitution of an upper selective permanent form of collapse of the permanently destroyed upper lobe should be considered. The lower lobe can then be conserved. Some functioning lung on both sides provides a great factor of safety for all patients with pulmonary disease.

At the present time 121 thoracoplasty patients included in this report have returned to work. We have been impressed with the fact that comparatively few complain of dyspnoea on exertion or show other evidences of pulmonary deficiency. A number of patients who preoperatively had had tightness in the chest, wheezing or slight dyspnoea on exertion found that these symptoms disappeared following thoracoplasty. A study of the lung volume and vital capacity in a series of 32 patients treated with thoracoplasty and lung mobilization has been recently made by Harter, Overholt and Perkins (7). The final determinations were made several months postoperatively. The patients were ambulatory or had returned to work when the postoperative determinations were made. Variations in values were found in both directions. The majority of patients showed a slight decrease in functional residual air. From this study it was concluded, however, that thoracoplasty, *per se*, does not leave the patient worse off physiologically than he was before the operation was performed. (See figures 9, 10, 11 & 12.)

## SUMMARY

A survey of the results so far obtained in 370 patients treated by 763 stages of thoracoplasty has been made. Mortality figures for this group have been given. It has been shown that the number of seriously ill patients accepted for thoracoplasty has been increased, yet the risk of operation has steadily declined. A practical form of classification has been worked out which has aided in the evaluation of results. Of the 370 patients, 206 were considered good chronics with the disease so located that a reasonably good chance of a satisfactory collapse was anticipated. One hundred and sixty-four patients with progressive disease,

empyema or extrapulmonary complications were given the benefits of thoracoplasty. Of those in the poor risk group 60 had bilateral cavitation. A high per cent (89.5 per cent) of the patients in the "good chronic" group were definitely benefited by the procedure. Slightly over half, 51 per cent, were already back at work and 25 per cent more were in various sanatoria with their disease quiescent or arrested. In the poor risk group 24 per cent were working and 26 per cent were quiescent or arrested. It was found that 69 per cent were benefited by operation. In the entire series 121 patients were completely rehabilitated. The possibilities are good that eventually 248 (80 per cent) of the 307 completed patients will be classified as apparently arrested and will be able to carry out varying degrees of activity.

Our experience with thoracoplasty in the treatment of patients with far advanced pulmonary tuberculosis suggests that it is the most valuable of all permanent collapse procedures. Selective, yet adequate collapse of diseased lung and conservation of uninvolved lung should be the ideal in permanent collapse therapy. The extent of the decostalization can be reduced by mobilization of the upper lobe at the time of the first-stage operation. A delay between stages is an important factor in planning the most conservative operation. Thoracoplasty is indicated not only for many good chronic patients but also has a place in the treatment of progressive and bilateral disease.

The author wishes to gratefully acknowledge the assistance given in the assembling of these data by the Superintendents and Medical Staffs of the following hospitals: The Barnstable County Sanatorium, Dr. Julius Kelley; The Bristol County Sanatorium, Dr. Garnet Smith; The Essex County Sanatorium, Dr. O. S. Pettingill; The Norfolk County Sanatorium, Dr. Nathan R. Pillsbury; The New Hampshire State Sanatorium, Dr. Robt. M. Deming.

## REFERENCES

(1) Brown, L., and Sampson, H. L.: The fate of the "good chronic" case of tuberculosis. A yardstick for the results of thoracoplasty, Tr. Nat. Tuberc. Assoc., 1934.

(2) Wiener, J. S., and Fishberg, M.: Ultimate results of thoracoplasty operations in pulmonary tuberculosis, Arch. Int. Med., 1933, *52*, 341.

(3) Matz, P.: End results of surgical treatment of tuberculosis, Amer. Rev. Tuberc., 1936, *33*, 533.

(4) Overholt, R. H.: Selective thoracoplasty in the treatment of pulmonary tuberculosis, Ann. Surg., 1935, *101*, 576.

(5) Overholt, R. H.: Thoracoplasty with lung mobilization, Amer. Rev. Tuberc., 1937, *35*, 411 and 430.

(6) Langmuir, A. D., Williams, S. L., and Pope, A. S.: Certain factors influencing the mortality of sanatorium treated cases of pulmonary tuberculosis, New England J. Med., 1934, *211*, 26.

(7) Harter, J. S., Overholt, R. H., and Perkins, H. J.: The lung volume after thoracoplasty, to be published in Jour. Thoracic Surg.

# ROENTGENOLOGICAL GROUP EXAMINATIONS FOR PULMONARY TUBERCULOSIS[1,2]

ROBERT G. BLOCH, BYRON F. FRANCIS, C. WESLEY EISELE AND ELWOOD W. MASON

## INTRODUCTION

The importance of roentgenological diagnosis in pulmonary tuberculosis has been ever increasing since the advent of the roentgen ray. It has now reached such magnitude that responsible physicians will not undertake to determine the exact extent of pulmonary disease and decide on the course of therapy by physical examination alone. But, more than that, no responsible physician will rule out the presence of pulmonary tuberculosis on the basis of negative physical findings. The experience that percussion and auscultation may fail even in extensive and advanced tuberculosis, although signaled by systemic and local symptoms, has been growing in recent years. It has convinced those working in this special field that certainly the small and beginning tuberculous lesions cannot be found without the aid of roentgenological examinations, and that many others which had been underestimated as to their extent and significance can be properly diagnosed only by this method.

So far this truth has failed to find the deserved recognition in medical practice. We know of no better way to describe the still prevailing conception of the diagnosis of pulmonary tuberculosis than by quoting the words of Kattentidt, one of the German pioneers in the work with which we want to deal in this paper. He writes (48) (translation), "Again and again and as a rule I encounter the opinion in all of the older colleagues that they can hear any pulmonary tuberculosis of consequence. This is the fundamental error. It has beset all those who have not had the opportunity to compare the findings of their ear with those of the roentgen ray; if they did have that opportunity, they would soon find that they heard tuberculosis where there was none and that they diagnosed health in the presence of advanced tuberculosis. These older

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

[2] Read at the Fifth International Congress of Radiology, Chicago, Illinois, September 12 to 17, 1937.

physicians finally now must recognize the true facts. If we lung specialists never trust our well-trained ear with the decision as to the presence or absence of pulmonary tuberculosis, then our colleagues who are not specialists should not find it too difficult to practice the same modesty." We are entirely in agreement with Kattentidt that failure to make a diagnosis of pulmonary disease because a roentgen examination was not carried out should be regarded as negligence.

Next to the inadequacy of physical examination it is the absence or scarcity of symptoms which is increasingly acknowledged as a cause of failure to diagnose tuberculosis. Really early tuberculosis, that is, tuberculosis of minimal extent, which has not advanced into the stage of tissue necrosis rarely causes noticeable symptoms. (We take this opportunity to state our opinion that pulmonary tuberculosis which has entered the stage of caseation and thereby of at least threatening excavation should never be classified as minimal regardless of how small the involvement may be.) The public is only inadequately served by early diagnosis campaigns urging individuals with certain symptoms to submit to an examination. The most such efforts can accomplish is to uncover cases of well advanced tuberculosis and not even very many of those. An amazing number of people with extensive and occasionally spectacular disease do not have enough symptoms to arouse the suspicions of the patient himself, his family, or even his physician. Again it was roentgenology which revealed this discrepancy.

These facts have been demonstrated by an imposing number of outstanding men in the field of tuberculosis. They have proved by figures, chiefly from Germany and the United States, how many cases of tuberculosis which had been missed entirely on physical examination were recognized by roentgenological examination. The results which recently were extensively reviewed by Kayser-Petersen (49) indicate that from ten to sixty per cent of all cases of tuberculosis which were found on roentgenological had been missed on physical examination. This estimate does not include the vast number of patients whose roentgenological findings surpassed the physical examination in demonstrating the size and extent of pulmonary disease. Five years ago we (Bloch 8) estimated, on the basis of the experience of our clinic, that about one-third of all cases of clinically important pulmonary disease are missed on physical examination. Now we believe that one-third is too conservative an estimate. We may mention the careful study of Sampson and Brown (74) on 1,004 patients at Trudeau Sanatorium in which they found

no physical signs of disease in 39.6 per cent and physical signs indicating less disease than the roentgenogram in an additional 36 per cent.

The only logical conclusion is that in order to find the disease at an early stage, to find it reliably at any stage, it is imperative to apply roentgenological examinations routinely to large groups of apparently healthy persons.

## TECHNIQUE

The growing recognition of this need by specialists in tuberculosis has in recent years led to an increasing number of roentgenological group examinations in many countries. Before attempting to summarize the results, it may be well to discuss briefly the technique of such examinations.

The great majority of all examinations among adults was made by fluoroscopy. The value of this method has been questioned by many. It has been called unreliable as too subjective because of technical difficulties, limitation of time, and fatigability of the examiner. The reports of failure to recognize tuberculous lesions subsequently diagnosed by roentgenograms range from less than 3 per cent to 33 per cent. It seems that the percentage of failures diminishes with the increasing experience of the examiners. The superiority of the roentgenogram over fluoroscopy cannot be questioned, but the expense has made it impracticable for many group examinations. Most authors agree that excellent results can be obtained by taking roentgenograms of all persons with definite or suspicious findings by fluoroscopy, and that success depends upon how freely the film can be used for that purpose. This has been our experience too. We do not believe that many tuberculous lesions of clinical importance are overlooked by an experienced examiner who is trained in fluoroscopic technique and in pulmonary pathology. This is also the opinion of Amberson (2B), Weber (88, 89), McCain (60), and Fellows (25, 26, 27), who has had an extensive experience with this method. Hetherington and Flahiff (42) believe that the more extensive and important lesions will be recognized by fluoroscopy as will also apical infiltrations extending below the clavicle.

Lesions are most easily missed in the upper subapical region where foci are obscured by the bones of the shoulder and by ribs. However, even a good roentgenogram may fail to reveal small infiltrations there. It should be emphasized here that the fluoroscopic examination is used only as a screen in case-finding surveys but never to rule out the possi-

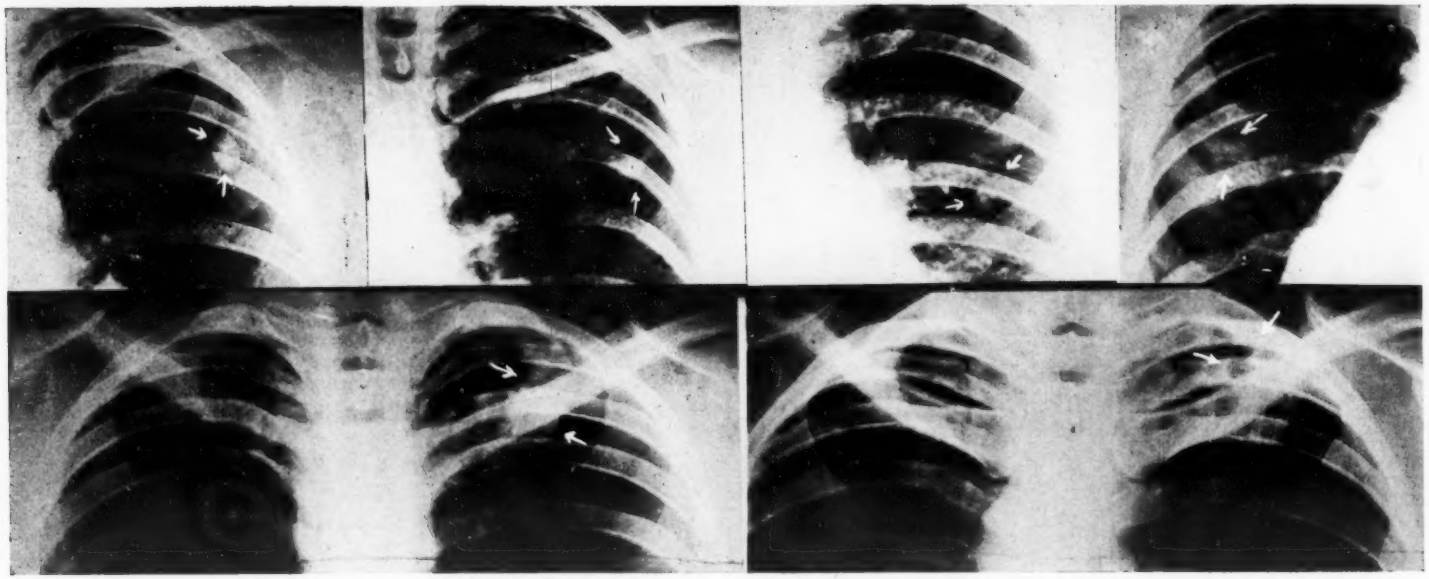


FIG. 1. Examples of small tuberculous lesions found by fluoroscopy

bility of pulmonary disease when there are symptoms. Nor is it reliable for making a definite diagnosis or as a means of following the course of a tuberculous lesion.

Figure 1 shows some of the small tuberculous involvements which were recognized during our own fluoroscopic examinations. Certainly all advanced tuberculosis can be diagnosed quite easily this way. The time which is required for the examination of one person depends upon the ability of the examiner to see and interpret shadows in the lung field. Like Kayser-Petersen, of Germany, we found that 30 seconds were sufficient for well accommodated and trained eyes to examine with satisfactory results. Long and tedious scrutiny is not the expression of greater caution, certainly not of greater ability. We find that one physician can examine from 50 to 80 persons at a time without tiring and impairing the accuracy of his findings.

Tuberculin tests instead of fluoroscopy have been employed as a screening method, chiefly in the United States—mainly in examining groups of children but also in some adult groups. We do not want to enter into an academic discussion of the value of tuberculin tests in supposedly healthy adults. Apparently they can be used successfully in children, but we have grave misgivings about the usefulness of tuberculin in adult groups. We doubt that it equals the fluoroscopic method in reliability and efficiency. Because of the high incidence of positive tuberculin reactions in most adult groups, a very high percentage of the tested individuals require roentgenograms. It is, therefore, more economical to use a roentgenological method from the beginning.

The very inadequate funds available for case finding should be used to yield maximum results. Hetherington and Flahiff (42) found that, when the cost of films is important, fluoroscopy is a more efficient screener than tuberculin-testing, that is, a higher proportion of those selected for films will have significant lesions. Amberson (2) recommends the tuberculin test as a screen if the community is known to have a low incidence of infection, but the X-ray if there is a high incidence. Relative values in tuberculosis surveys have been given careful consideration by several individuals and institutions (50, 68, 24, 66, 58, 70). It is recommended that their findings be consulted before planning a case-finding program.

## TOTAL REPORTED RESULTS

In 1923 Alder used fluoroscopy as a routine examination of recruits and drafted men in the Swiss Army. So far as we can determine, this

was the first practical use of serial roentgenological examinations. In that year, 2,000 recruits and 1,250 drafted men were examined, and of this group 68, or 2.1 per cent, were "mustered out" because of abnormalities which were found. This work of Alder's was referred to in 1930 by Walther (86) but not reported by Alder until 1936 (1). Before this, in 1902, Béclére and Solet (72) used the fluoroscope upon the recruits of a Battalion of the French Army and pointed out the relative frequency of intrathoracic abnormalities. The first reports of group examinations, on a larger scale, are available of school children and university students. Aside from a very few far-seeing and admirable efforts in the commercial and industrial field, the way to this new public health undertaking was shown by the universities. During very recent years, the method has been applied in examinations of professional, military, industrial and general population groups.

It is not the purpose of this paper to analyze in detail the results reported from these sources. This has been done very recently by Kayser-Petersen (49). His splendid monograph reviews the entire field of roentgenological group examinations and deserves reading by all who are interested in the subject.

We have tabulated (table 1) in some detail the results of group examinations available in the medical literature. We were interested in determining the incidence of active tuberculosis in the groups examined. This was difficult, not only because the criterion of activity differs so widely among examiners, but also because they chose to use so many different terms in which to express their findings. Some authors classify all latent or asymptomatic tuberculosis of the reinfection type as active, others only those associated with symptoms. Some use the terms "active" and "suspiciously active," others "manifest," "latent," etc. Obviously a certain percentage, possibly high, of the latent or suspiciously active will later manifest themselves either by symptoms or by changes on subsequent roentgenograms and thus fall within the "active" group. It has not, therefore, been possible for us to express the reported findings in any single term in general use. For this reason we have tried to include under the term "significant" those cases from the literature which seem to represent types of tuberculous lesions which we thought the authors considered important. In general, these would be types requiring of the patient some modification of his mode of life ranging from periodic observation and slight reduction in physical activity to immediate hospitalization.

The same type of lesions has not the same significance in different age

## TABLE 1

*Detailed tabulation of results reported in the literature*

| | GROUP | AGE | NUMBER OF REPORTS | TOTAL NUMBER EXAMINED | NUMBER EXAMINED BY FLUOROSCOPY | NUMBER EXAMINED BY ROENTGENOGRAMS | NUMBER OF TUBERCULIN TESTS | NUMBER OF SIGNIFICANT LESIONS | SIGNIFICANT LESIONS | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *per cent* | |
| | Children | | | | | | | | | |
| | Grade | | | | | | | | | |
| 1 | U. S. (9, 38, 46, 51, 7, 87, 43, 61, 90, 89, 88) | 5–14 | 11 | 30,445 | 393 | 5,785 | 28,908 | 62 | 0.20 | |
| 2 | Mass. 10 yr. plan (69) | Gr. children | | 140,000 | | 140,000 | 140,000 | About 140 | 0.10 | Active, 2.5% had reinfection type, 0.5% of high school group had active disease |
| 3 | Europe (49) | Up to 15 | 17 | 82,480 | 82,480 | | | 162 | 0.19 | Active |
| | | | | 252,925 | | | | 364 | 0.144 | |
| | High School | | | | | | | | | |
| 4 | U. S. (10, 54, 66, 21, 45, 77, 89, 11) | 14–20 | 10 | 33,851 | 2,586 | 17,514 | 20,074 | 200 | 0.57 | |
| 5 | Europe (75, 31, 49) | | 15 | 38,759 | 38,759 | | | 168 | 0.43 | Active, youths, majority older than U. S. high school group |
| 6 | Europe (Parretti) (49) | | | 11,508 | 11,508 | | | 201 | 1.74 | Active |
| 7 | Europe (Poland) (49) | 16 and 17 | | 638 | 638 | | | 22 | 3.45 | |
| | | | | 84,756 | | | | 591 | 0.70 | |
| | College Students | | | | | | | | | |
| 8 | U. S. (82, 80) | | 7 | 38,932 | | | | 262 | 0.67 | 1932–33, 7 colleges reporting, for variation in percentage see ref. (28) |
| 9 | Germany (49, 56, 47) | | 12 | 33,653 | 33,653 | | | 199 | 0.59 | Active |
| 10 | Europe (outside Germany) (20, 49) | | 11 | 19,702 | 19,702 | | | 307 | 1.50 | Active, 0.8% open |
| | | | | 92,287 | | | | 768 | 0.83 | |
| | Post-graduate | | | | | | | | | |
| 11 | U. S. (44, 41, 78) | | 4 | 4,766 | | 4,766 | | 101 | 2.10 | Medical and nonmedical students |
| | Teachers | | | | | | | | | |
| 12 | U. S. (84, 37) | | 2 | 5,451 | | 2,158+ | 4,067 | 119 | 2.18 | |
| 13 | Europe (49) | | 2 | 563 | 563 | | | 5 | 0.89 | Active |
| 14 | Europe (Russia) (49) | | | 653 | 653 | | | 52 | 7.90 | |
| 15 | Europe (Nuns) (49) | | | 1,231 | 1,231 | | | 57 | 4.60 | |
| | | | | 7,898 | | | | 233 | 2.95 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nurses and hospital employees | | | | | | | | | |
| 16 | U. S. (57) | | 1 | 1,567 | | 1,567 | | 50 | 3.20 | Glenn Lake Sanatorium, Minn. |
| 17 | U. S. (Belleview, N. Y. C.) (2) | | 1 | 492 | | 492 | 492 | 7 | 0.95 | Per 100 nurses per year (number developing tuberculosis during training period) with positive sputum, 3.7% with parenchymal lesions, nurses and employees of insane asylum |
| 18 | U. S. (Minnesota) (15) | | 1 | 2,430 | | 1,711 | 2,430 | 16 | 0.66 | |
| 19 | Europe (49) | | 4 | 1,419 | | | | 12 | 0.85 | |
| | | | | 5,908 | | | | 85 | 1.44 | |
| | Contacts | | | | | | | | | |
| 20 | U. S. (adults) (76, 39, 5, 24, 22, 89, 70) | | 7 | 5,871 | | | | 539 | 9.20 | |
| 21 | U. S. (children) (76, 11, 90, 51, 70) | | 4 | 4,901 | 43,245 | | | 72 | 1.60 | |
| 22 | Europe (23, 49) | | 3 | 43,245 | 15,331 | | | 5,191 | 12.00 | Family, friend-contact, all ages |
| 23 | Europe (Thürigen) (49) | | 1 | 15,331 | | | | 588 | 3.80 | |
| | | | | 69,348 | | | | 6,390 | 9.20 | |
| | Military | | | | | | | | | |
| 24 | U. S. (Overseas) (85) | | | 9,080 | | 9,080 | | 36 | 0.40 | |
| 25 | U. S. (C.C.C., White) (85) | | | | | | | | 1.80 | Number of men examined not given in article, percentage derived from statement that 73 per 1000 whites and 55 per 1000 Negroes had tuberculosis of which ¼ classified as active |
| 26 | U. S. (C.C.C., Colored) (85) | | | | | | | | 1.30 | |
| | Europe | | | | | | | | | |
| 27 | Police (49) | | 5 | 13,743 | 13,743 | | | 36 | 0.26 | |
| 28 | S. A. (Germany) (49) | | 11 | 18,837 | 18,837 | | | 155 | 0.82 | |
| 29 | Work Army (Germany) (49, 17) | | 18 | 27,131 | 27,131 | | | 76 | 0.28 | |
| 30 | France (49, 72) | | | 280,075 | 280,075 | | | 419 | 0.14 | Open cases { Most reports give "open" cases only, but in few in which "closed active" cases are reported percentage rises to 1.0 or above |
| 31 | Spain (49) | | | 2,260 | 2,260 | | | 12 | 0.50 | |
| 32 | Holland (49) | | | 1,101 | 1,101 | | | 4 | 0.36 | |
| 33 | Germany (32, 49) | | | 38,041 | 38,041 | | | 64 | 0.17 | Franz & Mudler, 1931–32 |
| 34 | Germany (49) | | 6 | 7,463 | 7,463 | | | 28 | 0.37 | |
| 35 | Swiss (49, 86, 1) | | | 20,000 | 20,000 | | | 200 | 1.00 | |
| | | | | 417,731 | | | | 1,030 | 0.25 | |
| | Races | | | | | | | | | |
| 36 | Indians (87, 55, 53, 63, 73, 14) | | 6 | 5,362 | | 3,624 | 5,362 | 251 | 4.68 | |
| 37 | Negroes (19, 6, 12) | | 3 | 14,782 | | 14,782 | | 412 | 2.78 | Majority of these belong to a group on relief |
| 38 | Chinese (36) | | 1 | 1,007 | | 1,007 | | 63 | 6.30 | |
| 39 | Puerto Rico (67) | | 1 | 4,039 | (Positive reaction) | tuberculin | 4,025 | 92 | 2.27 | |
| | | | | 25,190 | | | | 818 | 3.25 | |

TABLE 1—*Concluded*

| | GROUP | AGE | NUMBER OF REPORTS | TOTAL NUMBER EXAMINED | NUMBER EXAMINED BY FLUOROSCOPY | NUMBER EXAMINED BY ROENTGENOGRAMS | NUMBER OF TUBERCULIN TESTS | NUMBER OF SIGNIFICANT LESIONS | SIGNIFICANT LESIONS | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *per cent* | |
| | Hospital and other inmates | | | | | | | | | |
| 40 | U. S. (insane & feeble-minded) (15) | Chiefly adults | 1 | 11,509 | | 11,424 | 11,509 | 243 | 2.10 | Open cases |
| 41 | U. S. Diabetics (110, 79) | | 2 | 1,555 | | 1,555 | | 55 | 3.55 | Chest roentgenograms routinely as they appeared for treatment over period of years |
| 42 | U. S. Maternity (70) | | 1 | 400 | | | | 16 | 4.00 | |
| 43 | Europe (49) | | 8 | 20,504 | 20,504 | | | 95 | 0.45 | Public home for mothers and children |
| 44 | Europe (49) | | 3 | 1,058 | 1,058 | | | 20 | 1.80 | Private home for mothers and children |
| 45 | Europe (insane) (49) | | 1 | 166 | 166 | | | 9 | 5.40 | 2.4% open |
| 46 | Europe (hosp. non-tbc.) (49) | | 1 | 886 | 886 | | | 25 | 2.80 | |
| 47 | Europe (49) | | 9 | 8,439 | 8,439 | | | 43 | 0.50 | 19 cases open (homeless, indigent, blood donors, gymnasts) |
| 48 | Europe (polyclinic) (49) | | | 9,936 | | 9,936 | | 20 | 0.20 | "Frühinfiltrate" |
| 49 | Europe (stomach fluor.) (49) | | 1 | 2,000 | 2,000 | | | 26 | 1.30 | Cavities in 0.45% |
| 50 | Europe (lupus patients) (49) | | | 773 | 773 | | | 56 | 7.20 | 27.5 to 65.3% had tuberculous changes |
| | | | | 57,226 | | | | 608 | 1.06 | |
| | Working Group | | | | | | | | | |
| | U. S. | | | | | | | | | |
| 51 | Unemployed (6, 77) | | 2 | 11,000 | | 11,000 | | 352 | 3.20 | 10,232 Negroes unemployed not included here but under "Races" |
| 52 | Food handlers (77, 59) | | 2 | 2,605 | | 2,065 | | 52 | 2.00 | |
| 53 | Industrial (26) | | | 32,001 | 32,001 | | | 695 | 2.20 | |
| | Europe | | | | | | | | | |
| 54 | Holland (13) | | | 23,228 | 23,228 | | | 54 | 0.23 | 0.2% "open", therefore higher % than 0.23 undoubtedly active |
| 55 | Tolar (83) | | | 3,925 | 3,925 | | | 14 | 0.35 | There were 8.4% more with fibrous and fibrocaseous tuberculosis |
| 56 | (49) | | 10 | 3,020 | 3,020 | | | About 53 | 1.75 | Not classified as active |
| 57 | Denmark (printers) (33, 34) | | | 1,786 | | 749 | 1,786 | 1 | 0.06 | Phthisic change in 50 (2.8%), inactive 49 |
| | | | | 77,565 | | | | 1,221 | 1.58 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | "Kataster" (entire villages) | | | | | | | | | | |
| | Europe | | | | | | | | | | |
| 58 | Children (49) | | 2 | 1,655 | | (Pirquet) | 1,424 | 29 | 1.75 | Primary and reinfection types | Other examinations of entire communities have been made in U. S. but results have been included under classifications given above |
| 59 | Adults (49) | | 3 | 1,681 | 1,681 | | | 22 | 1.30 | Active | |
| 60 | Russia (49) | All ages | | 2,000 | 2,000 | | | 48 | 2.40 | Degree of activity not stated | |
| 61 | Denmark (40) | 15 to 24 | | 1,294 | | | | 7 | 0.54 | | |
| | U. S. | | | | | | | | | | |
| 62 | New York (rural) (52) | | | 846 | | 846 | | 1 | 0.13 | 9 had reinfection type, 50 had primary infection type | |
| | | | | 7,476 | | | | 107 | 1.43 | | |

groups. Thus all lesions in grade and high-school children interpreted as a reinfection type have been considered as significant, whereas this is not true for many reinfection lesions found in persons who are usually classified as adults.

Many reports could not be used at all because of the vague manner in which the findings were presented. From others we have extracted figures for significant tuberculosis which are probably not strictly accurate because obviously the examiners had not kept, or had not troubled to give, definite figures but expressed their findings in very round numbers. These instances we have indicated in the "Remarks" column.

Attention should also be called to the fact that nearly all of the European reports are based upon fluoroscopy as a screening method. (We assume that many times this method was used as the sole roentgenological procedure, for definitive diagnosis and follow-up, as well as for screening.) In the United States, on the other hand, tuberculin-testing was used as a screening method in a high percentage of instances. There were also many roentgenographical surveys of groups without any preliminary screening.

This summary of the literature concerns well over one million persons who have been subjected to the group examination procedure. About one-fourth have been children up to the age of fifteen years. In addition to these reports actually in the literature, we know of some other group examinations now under way, chiefly in industrial concerns. Dr. G. H. Gehrmann, Medical Director of E. I. du Pont de Nemours & Company, in a personal communication informed us that they have made chest roentgenograms of all applicants for employment and of their regular employees at the time of their periodic examination for the last five years. They find it a highly valuable procedure from the standpoint of both the employees and the company. The method is being used in other industrial organizations and in several units of the United States military services (4). Sixty colleges (29) now have active modern antituberculosis programs in force. Also in many unnamed clinics and doctors' offices in the country routine roentgenological examination of contacts is practised and many cases of tuberculosis are found in this way. In the Chest Clinic of the University of Chicago we have followed this procedure during the past nine years.

Our own interest has centered in the examinations of adults, partly because we have no access to large numbers of children, but chiefly because we believe that the most direct assault against tuberculosis may be

made through the adult population (91). From tables 1 and 2 it is quite apparent that more tuberculosis is found in adults than in children. The incidence of active tuberculosis in adults in both Europe and America varies according to the social and occupational status of the groups. It ranges from as low as 0.13 per cent in a rural district (52) of the United States to 3.3 per cent in a large group of the unemployed white persons living in New York City (6). As a whole, the results obtained by a

TABLE 2

*Summary of results presented in table 1*

| GROUPS | TOTAL | | UNITED STATES | | EUROPE | |
|---|---|---|---|---|---|---|
| | Number examined | Significant lesion | Number examined | Significant lesion | Number examined | Significant lesion |
| | | *per cent* | | *per cent* | | *per cent* |
| Contacts | 69,348 | 9.2 | Adults 5,871<br>Children 4,901 | 9.2<br>1.6 | 58,576 | 9.8 |
| Racial: | | | | | | |
| Indian (American)<br>Negro (U. S.)<br>Chinese<br>Puerto Rico | 25,190 | 3.25 | | | | |
| Unemployed | 11,000 | 3.2 | 11,000 | 3.2 | | |
| Industrial | 63,960 | 1.12 | 32,001 | 2.2 | 31,959 | 0.38 |
| Teachers | 7,898 | 2.95 | 5,451 | 2.18 | 2,447 | 4.7 |
| Food handlers | 2,605 | 2.0 | 2,605 | 2.0 | | |
| Nurses | 5,908 | 1.44 | 4,489 | 1.63 | 1,419 | 0.85 |
| College and University | 97,053 | 0.89 | 43,698* | 0.83 | 53,355 | 0.95 |
| Military | 417,731 | 0.247 | 9,080+ | 0.4 | 408,651 | 0.24 |
| Children: | | | | | | |
| Grade, 5–13 | 252,925 | 0.144 | 170,445 | 0.1–0.2 | 82,480† | 0.19 |
| High School, 14–18 | 84,756 | 0.70 | 33,851 | 0.57 | 50,905† | 0.76 |
| "Kataster" | 7,476 | 1.43 | 846 (Rural N. Y.) | 0.13 | 6,630 | 1.6 |

* Includes 4,766 classified in table 1 as postgraduate students.

† Average age slightly higher.

variety of examining techniques and interpretations are strikingly similar for groups of equal social and occupational status in the various countries. An outstanding exception, however, is the low incidence (0.23 per cent) reported in some European industrial groups (13), as compared with the relatively high figure (2.2 per cent) in the United States. Many European examiners of industrial and military groups have reported their results in a manner which allows us to use only the percentage of open cases as the figure representing "significant" findings. This probably

accounts for some of the discrepancy. There are differences in age or social status within some groups themselves which probably account for differences in incidence. Thus the percentage of disease in adults in contact with tuberculin-positive children was 3.7 (89), but in a dispensary group of contacts it was 9.7 (76). Among 1,143 students of an eastern girls' school (28, 82, 16) there were no cases of tuberculosis discovered by X-ray, but among students in our larger universities the percentage lies between 0.5 and 1.0.

Most of the results range from slightly below 1 per cent to somewhat over 3 per cent. The exception which far exceeds these figures is 9.2 per cent in those who have been in contact with tuberculosis. This is almost three times the high figure of 3.2 per cent found in a socially underprivileged group, the unemployed of the United States (tables 1 & 2). It is interesting to note how practical experience proceeds to silence the theoretical discussions about the importance or unimportance of exogenous superinfection with the tubercle bacillus in adults. These group examinations clearly demonstrate how man-made, foolish and futile are health laws which try to determine the age when contact infection need not be seriously considered. There is no individual of any age in whom active pulmonary tuberculosis cannot develop if the infection by contact with open tuberculosis occurs over a long enough period and with sufficient massiveness and virulence. Certainly no age limit can be drawn between the late childhood and young adult age. Our experience suggests that a very considerable number, possibly most, of the tuberculous involvements of clinical consequence are acquired and developed during the young adult age. This too is the opinion of Opie and McPhedran (64, 62, 65), based upon extensive investigations of family and extrafamily contacts. We consider this one of the keys to the tuberculosis question and look upon the failure to examine roentgenologically the contacts of advanced, and particularly of open tuberculosis, as gross negligence.

The roentgenological group examinations in our own University were initiated in 1932 when a total of 2,297 persons, comprising students, staff members, and employees of the university clinics and some members of the nonclinical faculty, were examined by the staff of the Chest Clinic. Only medical and foreign students—the latter because of a high incidence of tuberculosis in preceding years and those with a history of exposure—received stereoscopic roentgenograms; the rest of the group was fluoro-

scoped.[3] The second group of 1,594 students was examined in 1934 by the student health services with the assistance of the Chest Clinic. Roentgenological examinations of all university students, hospital

TABLE 3

*Roentgenological group examination—Classification of positive findings*

| | |
|---|---|
| A. Extrapulmonary disease (cardiac) | |
| B. Definite involvement of the lungs | |
| 1. Nontuberculous | |
| (a) Clinically significant | |
| (b) Not clinically significant | |
| 2. Definite tuberculous involvement | |
| *Medical Classification* | *Class of Management* |
| (a) Active (the classification of the Natl. Assn. applied) | Treatment |
| (b) Strongly suspicious of activity | Special observation (monthly) |
| (c) Possibly active (latent) | Routine observation (quarterly) |
| (d) Apparently inactive (including residuals of more recent pleuritis) | Routine observation (quarterly) |
| (e) Inactive (possibility of future reactivation considered) | Delayed observation (annual) |
| (f) Apparently healed (this includes old pleuritic residuals) | No observation required unless symptoms suggestive of lung disease arise |
| 3. Suspicion of tuberculous involvement | |
| (a) Strong suspicion of tuberculous involvement | |
| Suggestive { symptoms—indefinite / findings / history | Special observation |
| (b) Possibility of tuberculous involvement | |
| Vague { symptoms—indefinite / findings / history | Routine observation |
| (c) Remote possibility of tuberculous involvement | |
| Absence of { symptoms—indefinite / findings / history | Delayed observation |
| Total | |

employees, and staff members have since become an accepted routine with the University Health Services. Only the group of 1932 is presented in detail.

[3] Stereoscopic roentgenograms were taken of all in whom any kind of lesion was seen or suspected, small calcified foci (Ghon's tubercle) excluded.

One of the criticisms against the group method has been that it increases the possibility of overdiagnosis and may create an army of neurasthenics and hypochondriacs. We agree with Braeuning, of Germany, that group examinations will convince many who believe themselves sick that they are not; but, it is likely that insufficiently

TABLE 4

*Results of examinations at the University of Chicago*

Summary of roentgenologic group examinations

| CLASSIFICATION OF POSITIVE FINDINGS | 324 STUDENTS ROENTGENOGRAMS | | 962 STUDENTS FLUOROSCOPIES | | 1,011 ADULTS FLUOROSCOPIES | | TOTAL 2,297 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number | Per cent | Number | Per cent | Number | Per cent | Number | Per cent | |
| A. Extrapulmonary (cardiac) | | | 13 | 1.35 | 10 | 0.98 | | | |
| B. Definite involvement of lungs | 36 | 11.1 | 21 | 2.10 | 25 | 2.50 | 82 | 3.56 | |
| 1. Nontuberculous | 2 | 0.62 | 3 | 0.31 | 1 | 0.09 | 6 | 0.26 | |
| a. Clinically significant | 1 | | 2 | | 0 | | 3 | 0.13 | |
| b. Clinically not significant | 1 | | 1 | | | | 3 | 0.13 | |
| 2. Definite tuberculous involvement | 29 | 8.95 | 12 | 1.24 | 22 | 2.17 | 63 | 2.74 | |
| a. Active | 4 | 1.23 | 0 | 0.00 | 5 | 0.49 | 9 | 0.39 | 1.21%* |
| b. Strong suspicion of activity | 3 | 0.92 | 0 | | 4 | 0.39 | 7 | 0.30 | |
| c. Possibly active | 6 | 1.84 | 2 | 0.20 | 4 | 0.39 | 12 | 0.52 | |
| d. Apparently inactive | 1 | 0.30 | 3 | 0.31 | 3 | 0.29 | 7 | 0.30 | |
| e. Inactive | 5 | 1.54 | 2 | 0.20 | 2 | 0.19 | 9 | 0.39 | |
| f. Apparently healed | 10 | 3.08 | 5 | 0.51 | 4 | 0.39 | 19 | 0.83 | |
| 3. Suspicion of tuberculous involvement | 5 | 1.54 | 6 | 0.62 | 2 | 0.19 | 13 | 0.56 | |
| a. Strong suspicion | 0 | | 0 | | 1 | 0.09 | 1 | 0.04 | |
| b. Possibility | 1 | 0.30 | 4 | 0.41 | 0 | 0.00 | 5 | 0.21 | |
| c. Remote possibility | 4 | 1.23 | 2 | 0.20 | 1 | 0.09 | 7 | 0.30 | |

* This figure, composed of groups 2 a-b-c, comprises the percentage of cases which are of great clinical importance, the individuals being classed as patients at the present time.

trained and over-zealous examiners have often exaggerated the pathological significance of their clinical findings.

We are facing a new problem. Through this work we deal chiefly not with patients complaining of symptoms, but with people who in almost all instances are entirely unaware of the possibility of sickness. Great caution and hesitancy in making the diagnosis of active tubercu-

losis is indicated in every person where the findings are not beyond doubt from the beginning. The activity of many tuberculous involvements cannot be determined by one roentgenological examination. Weeks and even months of clinical observation may be required to decide whether a patient is in need of treatment, of subsequent examinations only, or if he can be considered as clinically nontuberculous.

Our findings in the group of 1932 are tabulated in a dual classification (tables 3 & 4) which attempts to adjust clinical management to pathological findings. The considerable detail of this classification was found necessary for our own use. It has turned out after prolonged observation that all cases which on the clinical examination were classified as active, strongly suspicious of activity, or possibly active, had to be diagnosed as active. The total percentage of active tuberculosis was 1.2 per cent. The necessity of prolonged observation renders it impossible to consider the results of any group examination as complete and definite before a period of at least six months. In addition to pulmonary findings, abnormalities in size or shape of the cardiac shadow led to a definite suspicion of heart disease in some of those examined and was later confirmed in a considerable number.

## EXAMINATION OF PREGNANT WOMEN

The desire to widen the scope of our group examinations within the possibilities offered by the University of Chicago Clinics has led to the routine fluoroscopy of pregnant women since 1934. The experience that expecting mothers and subsequently their offspring are in especially grave danger from active or latent tuberculosis made the examination of this particular group appear an obvious medical necessity. There is an unfortunate discrepancy in general medical practice with regard to the management of tuberculosis in the pregnant woman. On one side there is a tendency to interrupt pregnancies indiscriminately for clinically insignificant or easily manageable disease and, on the other side, to allow patients with active and dangerous tuberculosis to give birth and to expose the infant to infection because they withheld information about past disease or because physical examination revealed no evidence of pulmonary lesions.

All patients attending the prenatal clinic of the Chicago Lying-In Hospital (maternity hospital affiliated with the University of Chicago Clinics) were invited to be fluoroscoped. Of the 6,298 patients attending the clinic from February, 1934 to April, 1937, 4,040, or 64 per cent,

reported for examination (table 5). All patients showing definite or suspected lesions by fluoroscopy were referred for stereoscopic roentgenograms. Seventeen patients in whom tuberculosis was suspected on fluoroscopy did not report for roentgenograms. Forty-three, or 1.06 per cent, of those who did appear for fluoroscopy were proved to have

TABLE 5

*Results of examination of expectant mothers at the University of Chicago*

| | NUMBER | PERCENTAGE |
|---|---|---|
| Attendance: | | |
| Total clinic patients | 6,298 | 100.0 |
| Reporting for fluoroscopy | 4,040 | 64.0 |
| Not reporting for fluoroscopy | 2,258 | 36.0 |
| a. No known tuberculosis | 2,209 | 35.2 |
| b. Known tuberculosis (history) | 49 | 0.8 |
| Findings: | | |
| 1. Clinically important tuberculosis proven by subsequent roentgenograms: | | |
| a. Active | 28 | 0.69 |
| b. Inactive | 15 | 0.37 |
| | 43 | 1.06 |
| 2. Suspicious findings, but patients failed to get roentgenograms* | 17 | |
| Summary: | | |
| Tuberculosis found on fluoroscopy | 43 | |
| Known tuberculosis (by history) | 49 | |
| Total tuberculosis | 92 | |

If the incidence of 0.69 per cent was maintained there were 15 additional cases of active tuberculosis undiscovered among the unfluoroscoped patients.

Additional findings:

1. 375 were suspected of having abnormal cardiac shadows and of these 158 (3.9%) were subsequently found to have organic heart disease.
2. Three cases of bronchiectasis and one each of substernal thyroid, calcification of thyroid, calcification of pleura, tumor of pleura, spontaneous pneumothorax.

* Four patients cancelled their Clinic registration when asked to have chest films taken.

tuberculous changes. Of these, 28, or 0.69 per cent, had active tuberculosis.

The fear of the diagnosis of pulmonary tuberculosis is particularly great among the pregnant women. One reason seems to be the desire to conceal past disease from the husband and his relatives. In this connection it is interesting and striking that 2,258 women did not report

for examination and that a considerable number of obstetric patients who had not been fluoroscoped were found to have tuberculosis later on. It seems probable to us that the percentage of active tuberculosis would have been higher if they had all been examined. In order to obtain fully satisfying results, these examinations will, in some way, have to be made obligatory. With regard to the diagnosis of clinical significance of tuberculosis, this group differs from all the others inasmuch as a decision of therapeutic procedure has to be made immediately in most cases.

In addition to tuberculosis, several nontuberculous pulmonary and extrapulmonary conditions were found. Organic heart disease was suspected and proved by subsequent investigations in 158, or 3.9 per cent, of the patients. It was suspected but not proved in about an equally large number.

## DISCUSSION

The evidence offered in the available statistics, while proving the usefulness of roentgenological group examinations in discovering tuberculosis, does not necessarily convince of the magnitude of the tuberculosis problem as it still exists. In recent years, the much publicized decline of the mortality rate from tuberculosis has led a large public to believe that the disease is getting well under control. Even considering the fact that it has moved from first to seventh place as a cause of death, it is still a tremendous factor in public health; the death rate in several racial groups and socially underprivileged parts of the population has not declined as noticeably. Furthermore, there is no assurance that the mortality from any infectious disease, therefore also from tuberculosis, may not rise again. In this connection it is interesting to note that preliminary reports from 26 states (71) indicate that the expected decline of the tuberculosis mortality rate in the United States did not occur in 1936. There is certainly no proof that the morbidity from tuberculosis has declined at a rate even approximating that of the mortality. But even if it has in countries where public health control is an established force, there are large parts of the world where an attack on the disease has hardly been attempted. In the United States, the fact alone that tuberculous disease causes such a high death rate in the Negro population would make it an acute problem. The roentgenological examinations of about 25,000 supposedly healthy persons of this group is, of course, hardly a beginning.

Among the white population, the serial tests on students, nurses, and similar professional groups, desirable as they are, are only an initiation to what will have to be done. The health of these groups does not constitute, and hardly suggests, the size of the tuberculosis burden to the general public. So far, at least in the United States, the comparative figures of individuals examined in the various groups are not proportional to their public health importance. In European countries considerable parts of the total young adult population are coming under tuberculosis control through examinations of military and other state-controlled groups. In this country, the access to comparable parts of the population is difficult. We have, for instance, for some time, tried to obtain permission to carry out fluoroscopic examinations of groups of industrial workers. It was our hope that by doing so we could add a more vivid demonstration of the desirability of the method to that already made in the above described groups. So far, we have not succeeded, chiefly because of the fear of employees to jeopardize their employment and wage-earning capacity. Employment is rated higher than the secure knowledge of one's health. It is deplorable that economically hard times do not permit the realization of the fact that there is much undiscovered tuberculosis, that much of it is bound to show its effects sooner or later, that by trying to avoid the problem now it will continue to present itself, little by little, with much severer damage to single individuals. It has been estimated by Kattentidt that in students the average case of pulmonary tuberculosis is found by group examination three years earlier than if one waits until the patient presents himself with symptoms. During those three years, his chances of recovery become greatly diminished, not to speak of the infection which he may spread to others during the period.

It is the inescapable demand of our time that, against all opposition, these examinations be made possible in all accessible groups. With the mounting convincing evidence of their value, we may eventually arrive at what German authors termed "Kataster" examinations, that is, surveys of the total population of entire districts. Until that hope can be realized, the examination of the most endangered groups, with subsequent testing of the contact persons of all those found to have tuberculosis, would lead us far toward the goal of eradicating the disease.

The figure of a total number of well over 1,000,000, or, if we allow for the unreported ones, perhaps approximately 2,000,000 examinations throughout the world, shows how far we are from that goal. At present,

we would be neither medically nor economically prepared for finding and caring for the number of undiscovered tuberculous individuals. A problem of enormous proportions will arise. On the basis of the available statistics, it is a conservative estimate that 1.5 per cent of the supposedly healthy adult population has active tuberculosis of the lungs. If this estimate is applied to the adult population of the United States which numbers about 84,000,000, it follows that 1,260,000 people with active disease need to be found and cared for medically and socially, not to speak of the tuberculosis which would be discovered in their children. Figuring on institutional care for all of these afflicted adults, the 95,198 beds which were reported in the Journal of the American Medical Association for December 7, 1935, as available for the tuberculous appear as a poor provision indeed. The metropolitan area of New York City alone would yield a number of patients sufficient to occupy all of those beds, and they are fully occupied already.

The lack of facilities for care, however, should not deter us physicians from the effort to find the disease. We cannot expect that everything can be made ready to receive our charges before we have begun to look for them. Facilities will be provided, will have to be provided, by public and private agencies at the rate at which they are confronted with the already developed demand. It has been the experience of those carrying out routine roentgenological examinations that the majority of the cases found are in the minimal stage (25) and thus more satisfactorily managed with rest at home. If collapse therapy is indicated, it may be instituted with a shorter period of accompanying bed-rest. This aspect would mitigate somewhat the dismal outlook for facilities for adequate institutional care.

At this time the medical profession is not ready to face its own diagnostic task. Examiners will have to be trained, roentgen equipment provided, and last but not least, the expense of the examination will have to be greatly reduced. With the greater utilization of existing roentgen equipment this might be accomplished. The private physician has it within his power to carry out very effective antituberculosis work by procuring a roentgenological examination of at least every one of his patients who has had contact with tuberculosis. As proved above, the greatest incidence is found in that group. It is chiefly the roentgenologist whose technical advice and diagnostic ability will be called upon greatly in this work. But the present rate of charges for chest X-ray examinations by X-ray laboratories in many parts of the country prohibits this

procedure in the ordinary family of contacts. A public agency must then supply this service if it is given at all.

## SUMMARY AND CONCLUSIONS

1. The great value of the roentgenological survey method of finding tuberculosis has been proved.

2. Fluoroscopy followed by roentgenograms in all cases of definite or suspected pulmonary pathology is a satisfactory method.

3. The reported results of roentgenological surveys have established that the incidence of tuberculosis varies depending upon the age, race and social, occupational or medical status of each group studied.

4. The groups yielding the greatest concentration of active tuberculosis are known and for most efficient antituberculosis work should have the case-finding methods applied to them. Case-finding efforts are not effective antituberculosis measures unless adequate provision for treatment and for the examination of contacts is made.

5. The groups in the United States arranged in order of diminishing incidence of tuberculosis are approximately as follows: contacts, Indians, Negroes, unemployed, industrial workers, school teachers, and food handlers with rates of 2 per cent or above; college students, military groups and children with an incidence of 1 per cent or below.

6. In our own surveys, out of 324 medical and foreign students examined with stereoscopic roentgenograms, 13, or 4 per cent, with significant lesions were found. Fluoroscopy of 962 college students showed 2, or 0.2 per cent, and 1,011 adult clinic employees revealed 13, or 1.28 per cent. Among 4,040 fluoroscoped expectant mothers there were 28, or 0.69 per cent, with active tuberculosis.

## BIBLIOGRAPHY

(1) Alder, A.: Die systematische Röntgendurchleuchtung in der Armee, Schweiz. med. Wchnschr., 1936, *17*, 135.

(2) Amberson, J. B., Jr.: Some case finding principles of practical significance, Tr. Nat. Tuberc. Assn., 1934, p. 204.

Case finding methods for the diagnosis of tuberculosis, Jour. Amer. Med. Assn., 1936, *107*, 256.

(3) Amberson, J. B., Jr., and Riggins, H. McL.: Tuberculosis among student nurses: A five year study at Bellevue Hospital, Ann. Int. Med., 1936, *10*, 156.

(4) Annual Report of Surgeon General U. S. A., 1936, p. 144.

(5) Barclay, W. S.: A study of tuberculosis contacts in families, Amer. Rev. Tuberc., 1932, *26*, 192.

(6) Barnard, Margaret W.: X-ray mass procedure applicable for the discovery of early tuberculosis in industrial groups, Amer. J. Pub. Health, 1934, *24*, 8.

(7) BARNARD, MARGARET W., AMBERSON, J. B., JR., AND LOEW, M. F.: Tuberculosis in adolescents: A study of 1000 school children in New York City made under the auspices of the Bellevue-Yorkville Health Demonstration in 1930, Amer. Rev. Tuberc., 1931, *23*, 593.

(8) BLOCH, R. G.: Die Wichtigkeit der Röntgenuntersuchung für die Erkennung der Lungentuberkulose, Münch. med. Wchnschr., 1932, *2*, 1900.

(9) BOYD, A. R. J.: The incidence of tuberculosis in children entering primary schools in Vancouver, B. C. An attempt to trace their sources of infection with a suggested new approach to case finding, Amer. Rev. Tuberc., 1936, *34*, 67.

(10) BRACHMAN, D. S.: Modern case finding in tuberculosis, Ibid., 1932, *26*, 89.

(11) BRIDGE, E., AND STOKES, A. M.: Dispensary examination versus school examination in discovery of tuberculosis in children, Ibid., 1933, *28*, 522.

(12) BROWN, P. K.: Tuberculosis control in a railway health insurance program, Amer. J. Pub. Health, 1935, *25*, 741.

(13) BURGER, G. C. E., AND VAN WEEL, J. G. A.: Über Röntgendurchleuchtung und Röntgenphotographie der Lungen, Zentralblatt, 1936, *75*, 287; 1936, *76*, 125.

(14) BURNS, H. A.: Tuberculosis in the Indian, Amer. Rev. Tuberc., 1932, *26*, 498.

(15) BURNS, H. A.: A study of the incidence of tuberculosis in State Institutions in Minnesota, Ibid., 1936, *33*, 813.

(16) CHADWICK, H. D.: Personal communication to Ferguson (28) July 7, 1931.

(17) Correspondent from Berlin. Group roentgenologic examinations for tuberculosis, Jour. Amer. Med. Assn., 1936, *107*, 1235.

(18) COURCOUX, A., BIDERMANN, A., AND BUCQUOY: L'examen médical des étudiants en médicine et des infirmières, Rev. Tuberc., 1934, *4*, 725.

(19) CRABTREE, J. A., HICKERSON, W. D., AND HICKERSON, VIRGINIA P.: Tuberculosis studies in Tennessee. A community study of the prevalence of tuberculosis in the Negro. A community study of the prevalence of tuberculosis in the Negro, Supplement to Amer. Rev. Tuberc., 1933, *28*, no. 6.

(20) CZEZASWKA, Z., GRABOWSKI, W., AND HORNUNG, S.: Ergebnisse der Reihenuntersuchungen an der Universität in Lwów in Jahre 1930, Zeitr. f. Tuberk., 1932, *66*, 38.

(21) DOOLITTLE, S. E.: A study of tuberculosis in one junior high school in Honolulu, Amer. Rev. Tuberc., 1931, *24*, 491.

(22) DOWNES, JEAN: A study of the risk of attack among contacts in tuberculous families in a rural area, Amer. Jour. Hyg., 1935, *22*, 731.

(23) DRESSLER, M.: Beitrag zur Umgebungsuntersuchung bei Lungentuberkulose, Schweiz. med. Wchnschr., 1935, *65*, 490.

(24) EDWARDS, H. R., AND UNZICKER, GRACE: A cost analysis of clearing tuberculosis family contacts, Milbank Memorial Fund Quart. Bull., 1934, *12*, 306.

(25) FELLOWS, H. H.: Significant active pulmonary tuberculosis in the apparently healthy adult: A study of 141 cases, Amer. J. Med. Sc., 1934, *188*, 533.

(26) FELLOWS, H. H.: A study of incidence of pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, *30*, 109.

(27) FELLOWS, H. H.: Value of the fluoroscope in pulmonary tuberculosis case finding, Amer. J. Pub. Health, 1935, *25*, 109.

(28) FERGUSON, L. H.: Sex as a factor in tuberculosis in college students, Tr. 30th Ann. Meeting Nat. Tuberc. Assn., 1934, p. 193.

(29) FERGUSON, L. H.: National Tuberculosis Association, 33rd Annual Meeting, Milwaukee, June 2, 1937.

(30) FITZ, R.: The problem of pulmonary tuberculosis in medical students, Tr. Assn. Amer. Phys., 1931, *46*, 241.

(31) FLETCHER, E.: The detection of presymptomatic tuberculosis in children, Lancet, 1932, *222*, 444.

(32) FRANZ AND MÜLLER: Ein Jahr Reihenröntgenuntersuchugen im Reichsheer, Deutsche med. Wchnschr., 1932, *20*, 769.

(33) GROTH-PETERSEN, E.: A tuberculin test made on 1800 printers, Acta. Tuberc. Scandinav., 1936, *10*, 111.

(34) GROTH-PETERSEN, E.: A survey of tuberculous changes of the lungs in 800 printers, Ibid., 1936, *10*, 131.

(35) HALFORD, F. I.: Tuberculosis in the Hawaiian: A study of school children of Hawaiian blood, Amer. Rev. Tuberc., 1933, *28*, 370.

(36) HALL, G. A. M., AND CHANG, C. P.: Latent pulmonary tuberculosis infections in Chinese adults of the professional classes, Ibid., 1934, *30*, 193.

(37) HARRINGTON, F. E., MYERS, J. A., AND LAVINE, IDA: Tuberculosis among employees of the Minneapolis schools, Jour. Amer. Med. Assn., 1935, *104*, 1869.

(38) HASTINGS, D. R.: The examination of the school child for tuberculosis in a rural community, Amer. Rev. Tuberc., 1933, *28*, 516.

(39) HAYWOOD, ELOISE, MORRISS, W. H., AND WILSON, G. C.: Incidence of tuberculosis in the families of a group of sanatorium patients, Ibid., 1933, *28*, 637.

(40) HELSTED, K.: Traek af Tuberkulosens Optraeden i Danmark, Ugeskrift for Laeger, Quoted by 5B, 1935, *97*, 196.

(41) HERMAN, N. B., BAETJER, F. H., AND DOULL, J. A.: Tuberculous infection in medical students, Johns Hopkins Hosp. Bull., 1932, *51*, 41.

(42) HETHERINGTON, H. W., AND FLAHIFF, E. W.: Fluoroscopy in tuberculosis case finding, Amer. Rev. Tuberc., 1933, *27*, 71.

(43) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: A further study of tuberculosis in public school children, Ibid., 1934, *29*, 142.

(44) HETHERINGTON, H. W., MCPHEDRAN, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Further study of tuberculosis among medical and other university students, Arch. Int. Med., 1935, *55*, 709.

(45) HEWITT, EDITH S., AND CUTTS, R. E.: The incidence of tuberculous infection among students of a high school, Amer. Rev. Tuberc., 1932, *25*, 525.

(46) JOHNSTON, J. A., AND CHADWICK, H. D.: A study of childhood tuberculosis in Detroit, Ibid., 1933, *28*, 244.

(47) KATTENTIDT, B.: Das dritte Jahr Pflicht-Thoraxdurchleuchtungen an den Münchner Hochschulen, Zeitr. f. Tuberk., 1932, *66*, 24.

(48) KATTENTIDT, B.: Tuberkuloseforderungen, München. med. Wchnschr., 1937, *84*, 645.

(49) KAYSER-PETERSEN, J. E.: Über Reihenuntersuchungen mit Röntgenstrahlen. Ergebnisse der gesamten Tuberkuloseforchung, 1937, *8*, 71. (Georg Thieme, Leipzig)

(50) KLEINSCHMIDT, H. E.: Relative values in tuberculosis case finding work, Amer. J. Pub. Health, 1934, *24*, 615.

(51) KORNS, J. H.: Tuberculosis in children: Case finding methods and results in Cattaraugus County, N. Y., Amer. Rev. Tuberc., 1933, *28*, 251.

(52) KORNS, J. H.: Tuberculosis in a rural population, Milbank Mem. Fund Quart. Bull., 1934, *12*, 47.

(53) KORNS, J. H.: Comparative tuberculosis findings among Indians and white persons in Cattaraugus County, N. Y., Ibid., 1936, *34*, 550.

(54) LEGGETT, ELIZABETH A., AND MYERS, J. A.: The incidence of tuberculous infection among the high school students of Morrison County, Minnesota, Ibid., 1932, *26*, 559.

(55) LONG, E. R., AND HETHERINGTON, H. W.: A tuberculosis survey in the Papago Indian Area of Southern Arizona, Supplement to Amer. Rev. Tuberc., 1936, *33*, 407.

(56) MALMROS, H., AND HEDVALL-LUND, E.: Aufgaben u. Methoden der Gesndheitsuntersuchungen unter besonderer Berückschtigung der Aufgaben u. Erfolge der Reihendurchleuchtungen, Studentischer Gesundheitsdienst. Bericht über die erste internationale Tagung der Studentenärzte, Leysin, June 2–4, 1933.

(57) MARIETTE, E. S.: The tuberculosis problem among nurses in a tuberculosis sanatorium, Tubercle, 1936, *18*, 103.

(58) MARQUETTE, B.: How to determine the emphasis of a community tuberculosis program, Amer. Rev. Tuberc., 1935, *31*, 591.

(59) MARTIN, C. D., PESAR, H. T., AND GOLDBERG, J. A.: A tuberculosis survey among 2000 foodhandlers in New York City, Ibid., 1934, *29*, 182.

(60) MCCAIN, P. P.: Tuberculosis among Negroes in the United States, Ibid., 1937, *35*, 25.

(61) MCCAIN, P. P., THOMAS, C. D., AND SUMNER, H. L.: Tuberculosis among rural and village school children in Buncombe County, (outside of Ashville), North Carolina, Amer. Rev. Tuberc., 1935, *32*, 150.

(62) MCPHEDRAN, F. M., AND OPIE, E. L.: The spread of tuberculosis in families, Amer. Jour. Hyg., 1935, *22*, 565.

(63) MONTGOMERY, L. G.: Tuberculosis among pupils of a Canadian school for Indians, Amer. Rev. Tuberc., 1933, *28*, 502.

(64) OPIE, E. L., AND MCPHEDRAN, F. M.: Exogenous tuberculous infection of adults. Marital tuberculosis, Arch. Int. Med., 1932, *50*, 945.

(65) OPIE, E. L., MCPHEDRAN, F. M., AND PUTNAM, P.: The fate of persons in contact with tuberculosis: The exogenous infection of children and adults, Amer. Jour. Hyg., 1935, *22*, 644.

(66) OWEN, ETHEL D.: Administrative problems in the case finding of tuberculosis, Amer. Rev. Tuberc., 1935, *31*, 584.

(67) PASTOR, J. R., OTERO, P. M., PAYNE, G. C., SANTOS, R. R., AND SILVA, E.: Tuberculosis surveys in Puerto Rico. II. A study of two urban communities, Puerto Rico J. Pub. H. & Trop. Med., 1934–35, *10*, 514.

(68) PLUNKETT, R. E.: Relative values in tuberculosis case finding, Amer. J. Pub. Health, 1934, *24*, 511.

(69) POPE, A. S.: The discovery and prevention of tuberculosis in the community: A progress report on the "ten year program" in Massachusetts, Jour. Amer. Med. Assn., 1931, *97*, 846.

(70) POPE, A. S.: Application of our knowledge of tuberculosis through case finding, Tr. Nat. Tuberc. Assn., 1935, p. 317.

(71) U. S. Pub. Health Reports, 1937, *52*, 587.

(72) RANVILLOIS, M. H., CRISTIAN AND LIÉGEOIS: Á propos du dépistage précoce de la tuberculose dans l'armée, Bull. l'Acad. de Méd., 3 series, 1934, *112*, 115.

(73) RICHARDS, W. G.: Tuberculosis among the Indians in Montana, Amer. Rev. Tuberc., 1932, *26*, 492.

(74) SAMPSON, H. L., AND BROWN, L.: Correlation of clinical and roentgenological observations in pulmonary tuberculosis, Radiol., 1934, *22*, 1.

(75) SAMSON, J. W., AND HEINRICH, BERTHA: Röntgenreihenuntersuchungen Schulentlassener, Zeitr. f. Tuberk., 1931, *59*, 414.

(76) SCHUMAN, C.: Contact as a factor in the transmission of tuberculosis, Amer. Rev. Tuberc., 1936, *34*, 85.
(77) SHURLY, B. R., AND BRACHMAN, D. S.: Latent sources of contact in tuberculosis, Ibid., 1936, *34*, 96.
(78) SOPER, W. B., AND WILSON, J. L.: Five years experience in the detection of adult type tuberculosis by roentgen-ray among students entering Yale University, Tr. Assn. Amer. Phys., 1935, *50*, 50.
(79) SOSMAN, M. C., AND STEIDLE, J. H.: Diabetic tuberculosis, Amer. J. Roentgenol., 1927, *17*, 625.
(80) STIEHM, R. H.: Tuberculosis among University of Wisconsin students, Amer. Rev. Tuberc., 1935, *32*, 171.
(81) SYDENSTRICKER, E., AND DOWNES, JEAN: Prevalence of tuberculous infection in a rural community in New York State, Milbank Memorial Fund Quart. Bull., 1933, *11*, 221.
(82) Third Annual Report of Tuberculosis Committee, Amer. Student Health Assn., Proceedings of 13th Annual Meeting, Chicago, December 28–29, 1933.
(83) TOLAR, V.: Tuberkulose-Untersuchungen der Batá-Angestellten. Zbl. für d. gesamte Tuberkuloseforschung, 1935, *42*, 90.
(84) Tuberculosis among teachers, Bull. Nat. Tuberc. Assn., 1936, *22*, 88.
(85) Tuberculosis in CCC Camps, Ibid., 1937, *23*, 89.
(86) WALTHER, H. E.: Die Röntgenuntersuchung der Stellungspflichtigen und Rekruten in der Schweizerischen Armee, Acta Radiol., 1930, *11*, 411.
(87) WARNER, H. J.: The incidence of tuberculous infection among school children on five Montana Indian Reservations, Amer. Rev. Tuberc., 1932, *26*, 507.
(88) WEBER, G. W.: Case finding with the fluoroscope: A study of parents, grade and high school children, Bull. Nat. Tuberc. Assn., 1936, *22*, 35.
(89) WEBER, G. W., MURPHY, K. M., AND HOLCOMB, F. W.: The intracutaneous tuberculin test and use of the fluoroscope in a county survey, Amer. Rev. Tuberc., 1935, *32*, 331.
(90) WEINTRAUB, W. L.: Tuberculin positive children observed for various periods up to five years, Ibid., 1936, *33*, 247.
(91) WHITNEY, JESSAMINE S.: High points of attack on tuberculosis, Tr. 30th Ann. Meeting Nat. Tuberc. Assn., 1934, p. 151.
(92) ROOT, H. F.: Association of diabetes and tuberculosis, New England J. Med., 1934, *210*, 1.

*The following articles although not referred to directly deal with the problem in hand:*

(93) BRACHMAN, D. S.: The value of the roentgen ray in apparently healthy children of school age, Amer. J. Roentgenol., 1933, *30*, 303.
(94) BRAEUNING: Das rechtzeitige Auffinden der Lungen-Tuberkulose und die Tuberculosis Inappercepta, Klin. Wchnschr., 1932, *11*, 401.
(95) DUBLIN, L. I.: The incidence of tuberculosis in the industrial population, Amer. J. Pub. Health, 1932, *22*, 281.
(96) DUNHAM, K.: The clinical value of the chest radiogram, Tubercle, 1935, *17*, 33.
(97) FALES, L. H.: A protest against the current conception of activity in pulmonary tuberculosis, Amer. Rev. Tuberc., 1933, *27*, 101.
(98) Foreign Letters, Jour. Amer. Med. Assn., 1934, *103*, 2041.
(99) KATTENTIDT, B.: Foreign Letters, Ibid., 1934, *103*, 423.
(100) KLEINSCHMIDT, H. E.: Observations on tuberculosis work in Germany, Amer. Rev. Tuberc., 1936, *33*, 549.

(101) LONG, E. R.: Tuberculosis in university students, J. Outdoor Life, November, 1933.
(102) LONG, E. R.: Modern measures in mass control of tuberculosis, Puerto Rico J. Pub. H. & Trop. Med., 1935, *10*, 417.
(103) MAXWELL, C. W.: Advantages of a roentgenological chest survey applied to recruits and overseas replacements of the United States Army, Amer. J. Roentgenol., 1927, *18*, 562.
(104) MYERS, J. A.: Types of tuberculous lesions found in the chests of students of nursing and medicine, Amer. Rev. Tuberc., 1933, *28*, 93.
(105) MYERS, J. A., AND WULFF, MARJORIE: Eleven years observation on tuberculosis among university students, Ibid., 1932, *26*, 530.
(106) MILLER, J. A.: The undergraduate teaching of tuberculosis, Ibid., 1935, *32*, 481.
(107) OLIN, H. A.: X-rays and health, Ill. Med. Jour., 1935, *67*, 76.
(108) REID, ADA CHREE: Tuberculosis case finding. Five years experience with fluoroscopy, Amer. J. Med. Sc., 1934, *188*, 178.
(109) SHEPARD, C. E.: Campaign against tuberculosis in college students, Amer. J. Pub. Health, 1935, *25*, 1118.
(110) VAUGHAN, H. F.: Public health and tuberculosis, Amer. J. Roentgenol., 1933, *30*, 300.

# THE WELTMANN SERUM COAGULATION REACTION[1,2]

## A Comparison with the Sedimentation Reaction and with Clinical Findings in Pulmonary Tuberculosis

S. A. LEVINSON AND R. I. KLEIN[3]

### INTRODUCTION

For many years investigators in the field of tuberculosis have grouped their studies along lines of specific and nonspecific reactions. Those who have emphasized specific reactions encountered the problem of antibody-amboceptor reactions, and the intensity of this combination in relation to various stages of tuberculosis. These serological reactions had enthusiastic supporters at their inception, but upon further study, the claims made by the various original investigators were not corroborated. Thus the value of the specific reactions in tuberculosis have not up to the present fulfilled the claims of their originators.

Study was, therefore, made in the fields of nonspecific reactions with the hope that by this method one would be able to differentiate exudative from productive processes. In other words, a reaction that would indicate inflammatory processes, tissue destruction, toxaemia and other factors, and which would help to give a better understanding of changes taking place in the development of the tuberculous process. We might mention the Matefy, Daranyi, Frisch, Starling, and Takata-Ara among numerous nonspecific reactions that have been recommended as diagnostic and prognostic indicators in tuberculosis. These reactions have for one or more reasons failed to be of aid in the study of tuberculosis. More recently the sedimentation reaction has been applied not only to tuberculosis, but to practically all disease conditions, and it seems, from a perusal of the literature, that this nonspecific reaction has had so many supporters, that one might be given the impression that the sedimentation reaction is almost a specific test for any disease to which it is applied.

[1] Presented at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] From the Departments of Pathology and Pediatrics, University of Illinois College of Medicine and Cook County Hospital, Chicago, Illinois.

[3] Mead Johnson Fellow.

When Weltmann (1) introduced his serum coagulation reaction in 1930, he claimed just two things; that his reaction indicates either an exudative or a fibrotic process. This means that, by using the Weltmann serum coagulation reaction, one is able to state only that the blood obtained from the patient in question indicates one or the other process; or a tendency for the pathological change to go in one or the other direction. Weltmann did not claim that his reaction is specific for any disease condition.

## TECHNIQUE

The Weltmann reaction is simple to perform, requires little apparatus, and the result can be read within twenty minutes after the serum is obtained. The test can be done in a doctor's office as well as in an institution. Although we (2) have described the technique of the test in a previous paper which dealt with our observations in various diseases in both children and adults, we shall repeat the technique here since all reports but one are in the foreign literature.

From a stock solution of 10 per cent calcium choride ($CaCl_2 . 6H_2O$) ten dilutions consisting of 0.1 per cent, 0.09 per cent, 0.08 per cent, 0.07 per cent, 0.06 per cent, 0.05 per cent, 0.04 per cent, 0.03 per cent, 0.02 per cent and 0.01 per cent are made up. These dilutions are numbered from one to ten beginning with the strongest concentration. Ten small test tubes, such as are used in the Wassermann reaction, are placed in a metal rack and numbered in order from 1 to 10. Into each tube is pipetted 5 cc. of the similarly numbered calcium chloride solution and 0.1 cc. of unhaemolyzed serum. The tubes are then shaken so that the contents are well mixed and placed in a boiling water bath for 15 minutes. They are then removed and the reaction can be immediately determined. The contents of the tubes may be clear, faintly opalescent, turbid, or there may be a flocculation. There is usually a sharp and easily noted difference between flocculation and turbidity.

The number of tubes in which coagulation occurs is designated by Weltmann as the coagulation band (C.B. of that particular serum). If there is a very slight or doubtful flocculation in one tube the reaction is interpreted as being intermediate between that tube and the one before it. In normal serum the first 6 tubes usually show flocculation. Sometimes there is a slight or doubtful flocculation in the seventh tube. The normal coagulation band is therefore 6 to $6\frac{1}{2}$ and is remarkably constant. This means that normal human serum diluted 50 times with

calcium chloride solution and heated in a boiling water bath for 15 minutes will not coagulate or flocculate if the concentration of the calcium chloride is less than 0.04 per cent. If the coagulation band is less than 6, Weltmann speaks of the reaction as showing a shift to the left, whereas, if the coagulation band is 7 or greater, the reaction indicates a shift to the right.

## MATERIAL STUDIED

Our material consisted of patients admitted to the Illinois Research and Educational Hospital and the Cook County Hospital. The coagulation band was determined by Weltmann's original technique and the sedimentation rate by the method of Wintrobe and Landsberg (3) so that the rate could be corrected in relation to the cell volume. We feel that at the present time Wintrobe and Landsberg's procedure is one of the more accurate of the numerous methods for determining the sedimentation rate. In tuberculosis, where various degrees of anaemia are so common, it appears to us that the uncorrected sedimentation rate can often be very misleading.

*Classification:* We have separated our cases into the following groups:

(*1*): General observations of the sedimentation rate and Weltmann reaction in three types of pulmonary tuberculosis in adults: (a) minimal; (b) moderately advanced; (c) far advanced pulmonary tuberculosis. In these groups, several determinations were made on each patient over a period of three to five months.

(*2*): Repeated observations, usually weekly, on selected cases.

(*3*): Daily observations made on selected cases for correlation studies of the Weltmann reaction, sedimentation rate, blood pH, carbon dioxide combining power, cholesterol and the clinical findings.

(*4*): Single observations on a number of cases.

We have indicated in chart 1 the serum coagulation reaction in several conditions which give opposite coagulation bands. In exudative conditions, as in lobar pneumonia, we find an extreme shift to the left and the coagulation band is almost always zero during the stage of consolidation. In septic states, and in malaria, the coagulation band is usually either normal, or shows a shift to the right. Cirrhosis of the liver, endocarditis lenta, and peritoneal carcinoma also give a shift to the right, whereas acute rheumatic fever, and peritoneal tuberculosis, give a shift to the left.

*Detailed analysis of the material studied:* Charts 2, 3 and 4 illustrate our findings in adult tuberculosis. Chart 2 represents the far advanced cases, chart 3 the moderately advanced cases and chart 4 the incipient cases. In each group the individual cases were arranged according to their Weltmann reaction which was correlated with the sedimentation rate done at the same time. Although several blood examinations were made in each case, we have recorded only the last one.

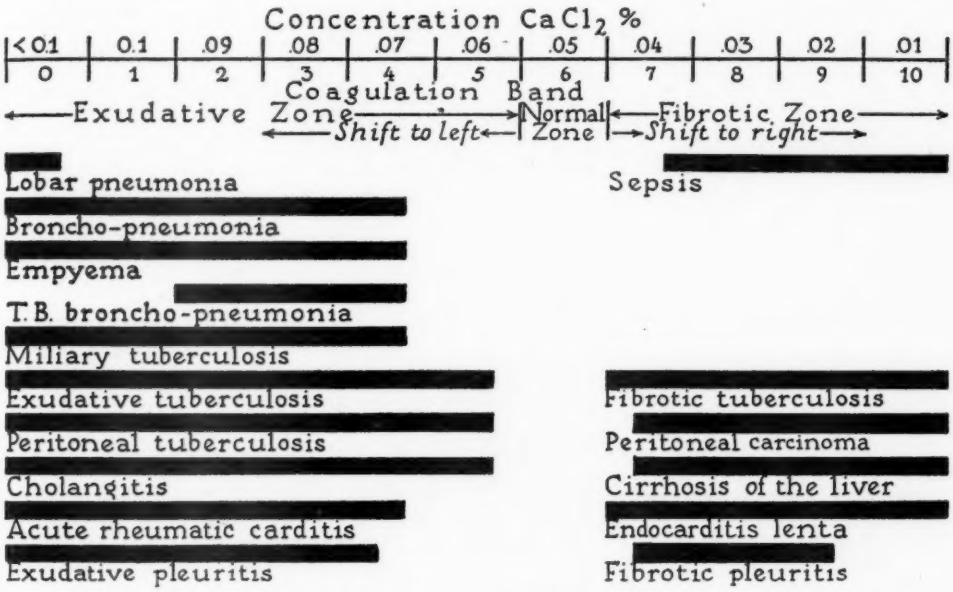



CHART 1. Range of the Weltmann reaction. Weltmann serum coagulation band in tuberculosis indicating the range in the exudative and fibrotic zones, as compared with pneumonia, heart disease and cirrhosis of the liver.

*Analysis of the cases of far advanced tuberculosis with Weltmann reaction and the sedimentation rate:* In chart 2 (52 cases studied) which represents the far advanced cases we find the sickest patients toward the left end of the chart where the coagulation band is low. The sedimentation rate in this group is rapid, and the death rate is high. Most of these patients were febrile and had positive sputa. At the right end of the scale, where the coagulation band is normal or increased, the death rate is relatively low, and most of the patients were clinically improving. The sedimentation rate in a large percentage of this group was rapid and did not correlate with the coagulation band, or the clinical status. Of the three

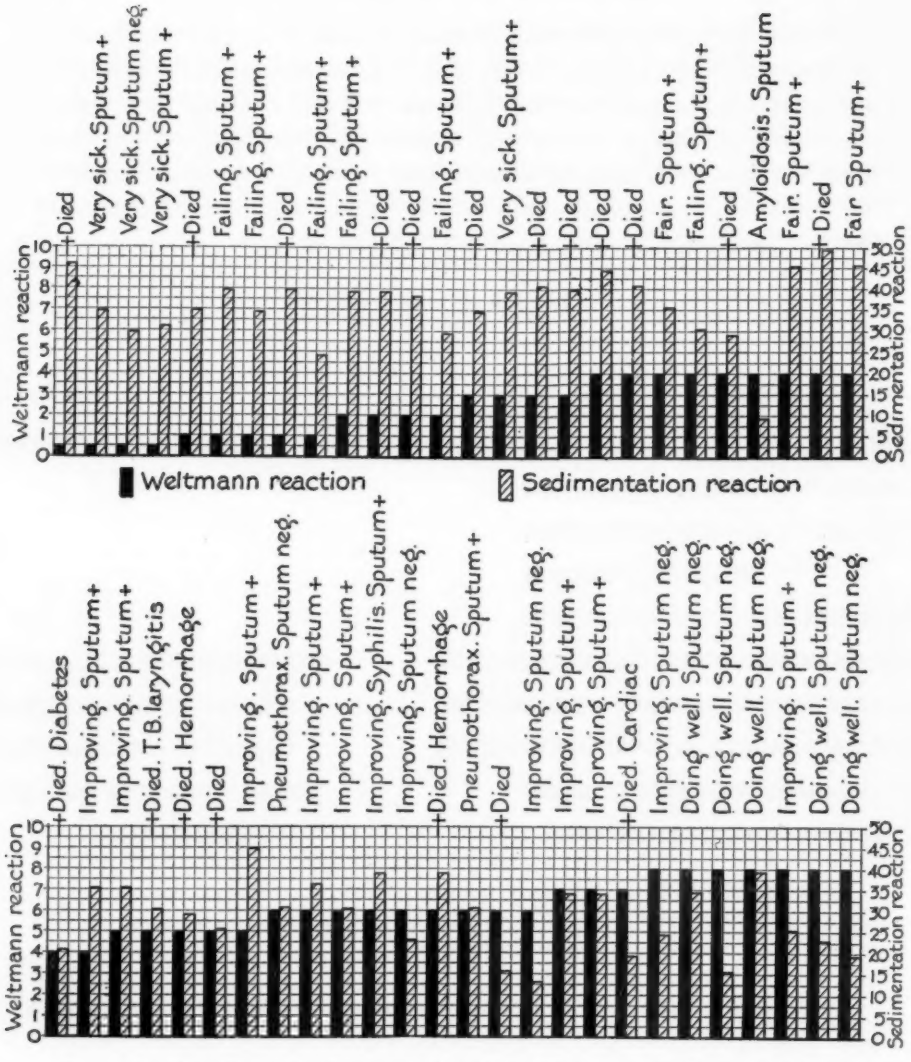



CHART 2. Far advanced pulmonary tuberculosis (52 cases studied) arranged from the lowest to the highest coagulation band, and compared with the sedimentation reaction. The solid column is the Weltmann reaction and the striped column is the sedimentation reaction. Each solid and striped column together is for a different patient. It is noted that the greatest number of deaths occurred in those patients in whom the coagulation band was in the left or the exudative zone.

deaths in this group one was due to pulmonary haemorrhage, one to coronary thrombosis, and the other patient died at home, so that the direct cause was not ascertained. Although the sedimentation rate was

rapid in the very ill patients in the far advanced group, it was also rapid in many of the quiescent cases with negative sputum, and did not compare as closely with the clinical state as did the Weltmann reaction.

*Analysis of the cases of moderately advanced tuberculosis with the Weltmann reaction and the sedimentation rate:* In the moderately advanced group of cases (30 cases) (chart 3) we again find that the most active cases are to the left and have low coagulation bands and relatively rapid

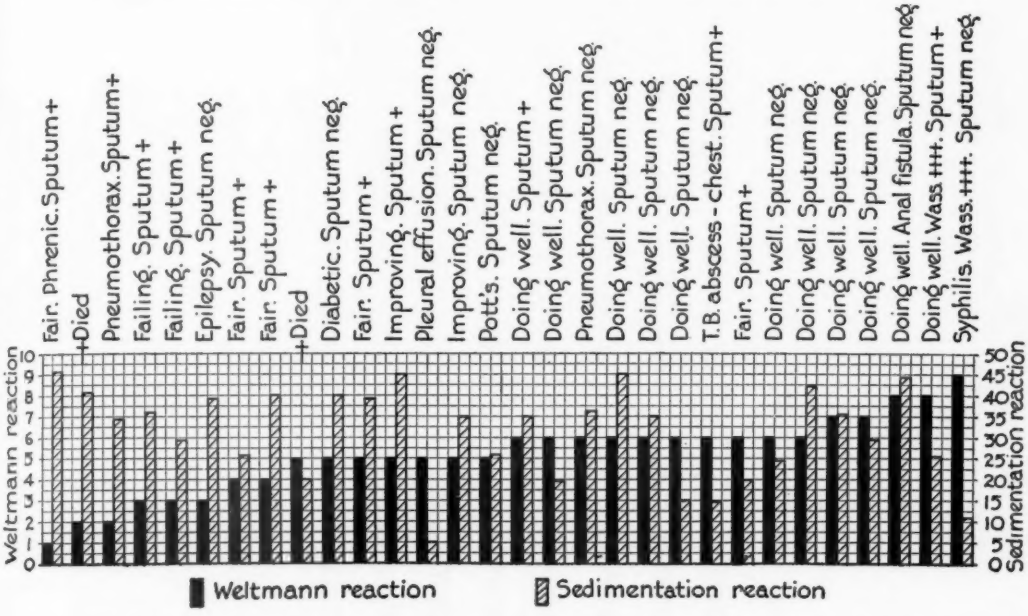



CHART 3. Comparison of the Weltmann reaction with the sedimentation rate in the moderately advanced group of pulmonary tuberculosis (30 cases studied). The solid column is the Weltmann reaction and the striped column is the sedimentation reaction. Each solid and striped column together is for a different patient. The sedimentation rate was rapid and the Weltmann reaction was within the normal range and to the right in about two-thirds of the cases examined.

sedimentation rates. Two patients in this group died when the coagulation band was normal or increased. Most of the patients were showing clinical improvement and had negative sputum. Some of these cases had normal sedimentation rates.

*Analysis of the cases of minimal tuberculosis with the Weltmann reaction and sedimentation rate:* Chart 4 illustrates our findings in the group of adults with minimal pulmonary tuberculosis; eight such cases were stud-

ied. All of the patients in this group did well, and were ultimately discharged as arrested cases. The lowest coagulation band in this group was five and the highest eight, and the sedimentation rate was rapid in four, and normal or only slightly increased in the other four patients.

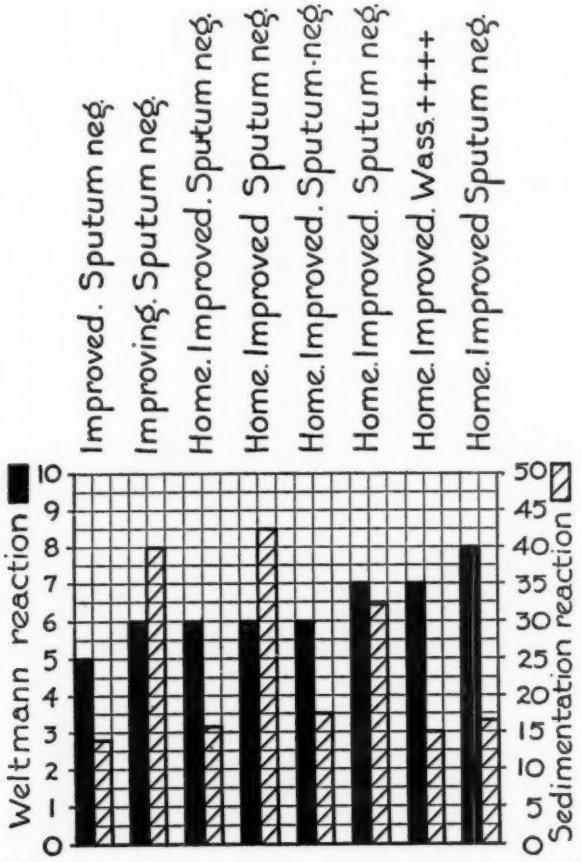

Improved. Sputum neg.
Improving. Sputum neg.
Home. Improved. Sputum neg.
Home. Improved Sputum neg.
Home. Improved. Sputum neg.
Home. Improved. Sputum neg.
Home. Improved. Wass. ++++
Home. Improved Sputum neg.
Weltmann reaction
0 1 2 3 4 5 6 7 8 9 10
Sedimentation reaction
0 5 10 15 20 25 30 35 40 45 50

CHART 4. Incipient or minimal pulmonary tuberculosis (8 cases studied). The Weltmann reaction compared with the sedimentation rate. The solid column is the Weltmann reaction and the striped column is the sedimentation reaction. Each solid and striped column together is for a different patient. Although the sedimentation rate was variable, the Weltmann reaction was normal or to the right.

From these observations we conclude that the coagulation band is decreased and the sedimentation rate is increased in the active moderately and far advanced cases of pulmonary tuberculosis. In the incipient and arrested cases the coagulation band is normal, or increased, while the

sedimentation rate may remain rapid. There is no definite correlation between the Weltmann and sedimentation reactions, and the former seems to be a better index of the clinical state of the patient.

We now proceed to an analysis of our results in a group of tuberculous children. Here we have compared the Weltmann coagulation band with the sedimentation reaction weekly over periods of two to five months. We wish first to contrast two cases of tuberculosis as recorded on charts 5 and 6.

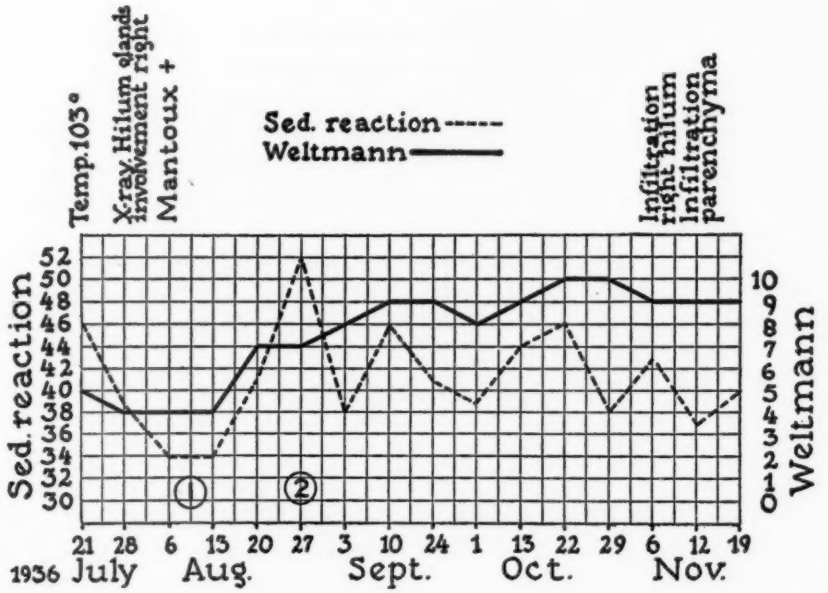

Temp. 103°
X-ray Hilum glands involvement right
Mantoux +
Sed. reaction -----
Weltmann ——
Infiltration right hilum
Infiltration parenchyma
Sed. reaction
52 50 48 46 44 42 40 38 36 34 32 30
Weltmann
10 9 8 7 6 5 4 3 2 1 0
1
2
21 28 6 13 20 27 3 10 24 1 15 22 29 6 12 19
1936 July Aug. Sept. Oct. Nov.

CHART 5. Primary pulmonary tuberculosis in a Negro girl thirteen years of age. The clinical improvement was reflected more accurately in the Weltmann reaction than in the sedimentation rate which was always rapid.

*Detailed study of individual cases of tuberculosis:*

Chart 5 refers to a 13 year old colored girl (*N. W.*) who was admitted to the hospital complaining of a poor appetite and loss of weight. Because of the fever and indefinite clinical findings, the diagnosis at first was thought to be typhoid fever or pyelitis. Later the Mantoux test was found positive, and the X-ray picture showed large hilar lymph nodes with a fuzzy infiltration in the right lung. The X-ray picture was repeated at a later date and it showed an infiltration of the right hilum which extended into the parenchyma of the lung. The temperature varied at the beginning from 103° to 104° and later dropped to 101°F. It remained at this level for a few weeks, and then became

normal and remained so until the patient was discharged from the hospital. The clinical diagnosis was primary pulmonary tuberculosis and the patient made a rapid clinical improvement. The Weltmann reaction at first showed a slight shift to the left and the sedimentation reaction was rapid as indicated by ① on the chart. As the patient showed clinical improvement, and the lesion in the lung became arrested, the Weltmann reaction returned to normal and then showed a shift to the right as indicated by ② on the chart; whereas, the sedimentation reaction was rapid throughout the stay in the hospital.

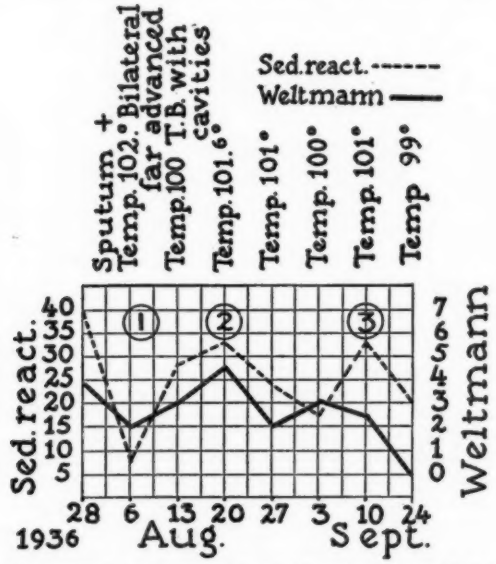



CHART 6. Rapidly progressive bilateral bronchogenic tuberculosis with cavitation with death in a Mexican girl eleven years of age. The Weltmann reaction persists in the exudative zone, and the sedimentation rate fluctuates.

If one were to use the Weltmann reaction as a guide in the progress of this patient's condition, it would indicate that the clinical course became arrested and that the early exudative changes were replaced by fibrotic processes. In other words, there was a correlation between the clinical improvement and the Weltmann serum coagulation reaction. The sedimentation reaction was rapid at all times, and if one were to rely on this test alone it would indicate that the patient still had an active tuberculosis. In this case there was no correlation between the Weltmann reaction and the sedimentation test.

In chart 6 we present the results obtained in the study of a Mexican girl (*J.*) eleven years of age, who had a rapidly progressive bilateral bronchogenic

type of tuberculosis with cavitation, and who died approximately eight months after the clinical onset of the disease. She was admitted to the hospital with complaints of loss of weight, cough, diarrhoea and fever for the past six months. Her sputum was positive, and when she was first seen the coagulation band was four and the sedimentation 38 as indicated by ① on the chart. Her clinical course was rapidly downhill and the coagulation band was always in the exudative zone ⑤ and reached zero before death ⑥. The sedimentation rate fluctuated, however, and approached the normal level several times.

In this case also the Weltmann reaction reflected the clinical state and the pathological process more accurately than did the sedimentation rate. It has been shown that in cachectic states and some overwhelming infections, such as peritonitis, the sedimentation rate may be normal. The coagulation band, however, has in our hands always been indicative of the pathological state.

The following example in chart 7 is that of a colored boy (*J. B.*) seven years of age, who came into the hospital with a temperature of 101°F. At this time the Weltmann reaction showed a slight shift to the left and the sedimentation reaction was rapid. The physical findings showed a right cervical adenitis, with râles in the right upper chest. As the Weltmann reaction shifted to the left in tube 3, as indicated by ① in the chart, the sedimentation reaction approached the normal limit, even though the patient's temperature still remained 101°F. The Weltmann reaction remained normal or slightly to the left throughout the period of observation ⑤; whereas the sedimentation rate fluctuated in the more rapid zones ⑥. The X-ray pictures showed first a consolidation in the upper half of both lungs. X-ray pictures taken about three months later still showed involvement in the upper half of the right lung. The patient is still in the hospital.

In this example there was not an absolute agreement between the Weltmann reaction and the sedimentation time.

Chart 8 represents a colored male (*A. T.*) two and one-half years of age. He was admitted to the hospital because of a history of contact with tuberculosis. The boy's mother has tuberculosis and is at the present time a patient in a tuberculosis hospital. The patient's temperature was 104°F. and the Mantoux test was positive. X-ray examination revealed an infiltration in the upper half of the lung field. Diagnosis of a primary tuberculosis with bilateral tracheobronchial adenitis with a secondary infiltration was made. The involvement in the left upper lobe was interpreted as epituberculosis.

On October 13, the patient's temperature was 104°F. and there was vomiting. No meningeal involvement was noted and examination of the spinal fluid was negative. The Weltmann reaction was normal as indicated by ① on the chart, and the sedimentation reaction was rapid. A few days later the patient presented slight rigidity of the neck. The spinal fluid showed 70 lymphocytes and the sugar was 63 mgm. per 100 cc. The Weltmann reaction showed a slight shift to the left and the sedimentation reaction was less rapid. On October 29, the patient showed clinical improvement, and the Weltmann

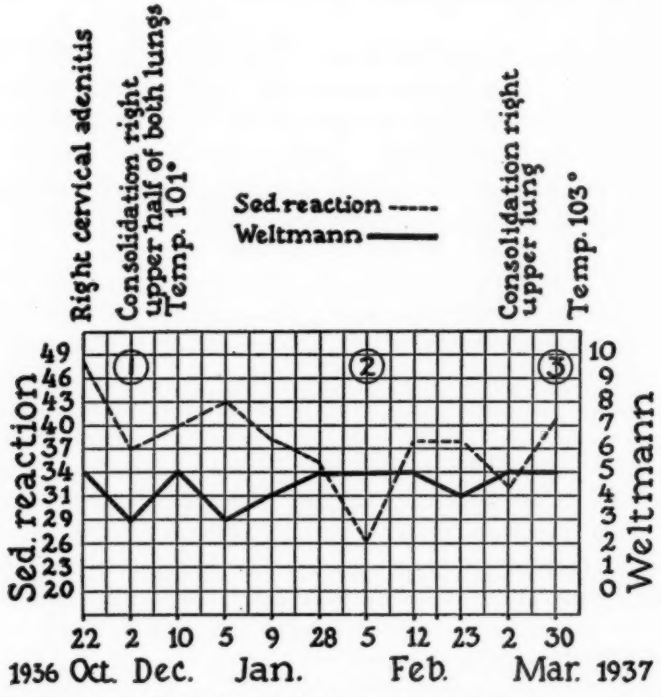

Right cervical adenitis
Consolidation right upper half of both lungs Temp. 101°
Sed. reaction -----
Weltmann ——
Consolidation right upper lung
Temp. 103°
Sed. reaction
49 46 43 40 37 34 31 29 26 23 20
Weltmann
10 9 8 7 6 5 4 3 2 1 0
① ② ③
22 2 10 5 9 28 5 12 23 2 30
1936 Oct. Dec. Jan. Feb. Mar. 1937

CHART 7. Right cervical adenitis with infiltration in both lungs. Negro boy seven years of age. There is somewhat of an agreement between the Weltmann reaction and the sedimentation rate.

reaction returned to normal ② but the sedimentation reaction remained rapid. The patient showed clinical improvement for the following month and the Weltmann reaction was not only normal but gave a shift to the right ③, whereas the sedimentation rate was persistently rapid. In the latter part of January the patient developed chickenpox, the Weltmann reaction at this time showed a slight shift to the left ④, and the sedimentation reaction was also rapid. Then in March, 1937, the patient started to vomit again. The spinal fluid was essentially negative. The Weltmann reaction showed a slight shift to the left, the sedimentation reaction was rapid. Toward the

end of March, 1937, the patient developed diarrhoea. The Weltmann reaction gave a marked shift to the left ⑤, the sedimentation rate was approximately normal.

This patient is still in the hospital, and although the X-ray examination at first showed an infiltration extending out from the hilum, the second X-ray film showed an infiltration in the upper half of the left

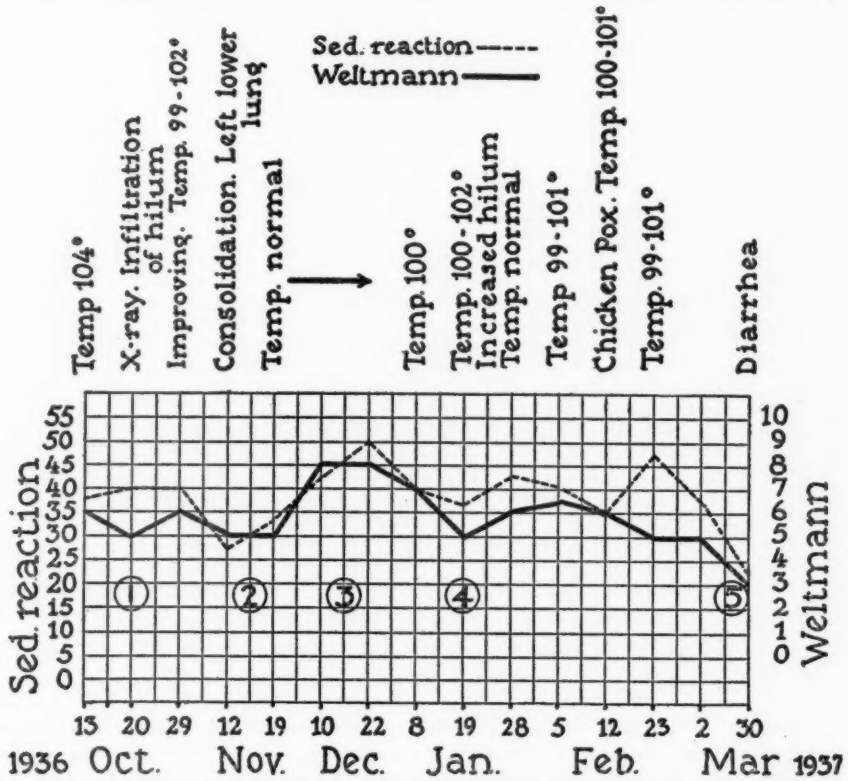

Sed. reaction
Weltmann
Temp 104°
X-ray. Infiltration of hilum
Improving. Temp. 99-102°
Consolidation. Left lower lung
Temp. normal
Temp. 100°
Temp. 100-102°
Increased hilum
Temp normal
Temp 99-101°
Chicken Pox. Temp 100-101°
Temp. 99-101°
Diarrhea
Sed. reaction
Weltmann
55 50 45 40 35 30 25 20 15 10 5 0
10 9 8 7 6 5 4 3 2 1 0
① ② ③ ④ ⑤
15 20 29 12 19 10 22 8 19 28 5 12 23 2 30
1936 Oct. Nov. Dec. Jan. Feb. Mar 1937

CHART 8. Primary tuberculosis with bilateral tracheobronchial adenitis and infiltration in left upper lobe. Negro boy two and one-half years of age. The sedimentation rate was most rapid when the Weltmann reaction was in the fibrotic zone and the patient was clinically improving.

lung. There was no agreement between the Weltmann reaction and the sedimentation time, and at times the sedimentation reaction was a better index than the Weltmann reaction.

Chart 9 is of a four year old white male (*W. W.*), who was admitted to the hospital in August, 1936, with a diagnosis of Pott's disease. Previous to admittance to the hospital, the patient was under observation by a physician

who diagnosed the pulmonary findings as a fibroid tuberculosis. The child developed anasarca, dyspnoea, cough and ascites. The urine showed a 2 to 4 plus albumin. On admission the Weltmann reaction gave a shift to the left, as indicated by ① on the chart and the sedimentation time was slightly rapid. Later the coagulation band was still to the left ② and the sedimentation reaction went to normal, and at this time X-ray examination revealed opacity in the right side of the chest with pleural effusion. There was a

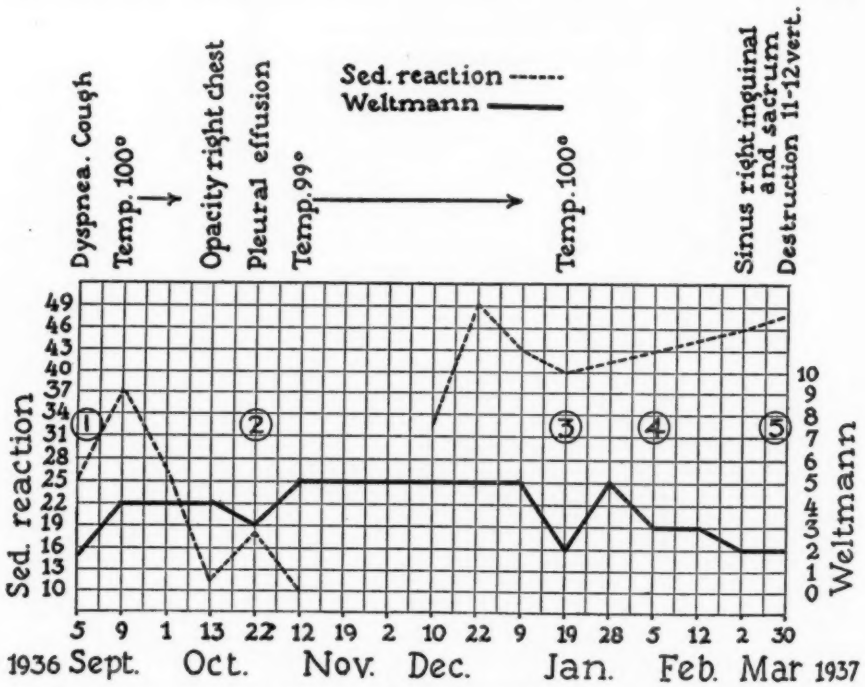

Dyspnea. Cough
Temp. 100°
Opacity right chest
Pleural effusion
Temp. 99°
Sed. reaction
Weltmann
Temp. 100°
Sinus right inguinal and sacrum
Destruction 11-12 vert.
Sed. reaction
Weltmann
49 46 43 40 37 34 31 28 25 22 19 16 13 10
10 9 8 7 6 5 4 3 2 1 0
① ② ③ ④ ⑤
5 9 1 13 22 12 19 2 10 22 9 19 28 5 12 2 30
1936 Sept. Oct. Nov. Dec. Jan. Feb. Mar 1937

CHART 9. Pott's disease with infiltration in the right lung and destruction of the eleventh and twelth dorsal vertebrae. White boy four years of age. The Weltmann reaction is in the exudative zone although the sedimentation rate becomes normal. Later the sedimentation rate increases with a more marked shift to the left of the Weltmann reaction.

slight improvement in the clinical condition of the patient ③ which was reflected in the rise of the coagulation band to 5. The Weltmann reaction later shifted to the left ④ and the sedimentation reaction became more rapid, and at this time X-ray examination still revealed opacity in the right side of the chest, and there was a destruction of the 11th and 12th dorsal vertebrae. The Weltmann reaction continued in the exudative zone ⑤ and the sedimentation rate was rapid. The physical findings at this time showed that the liver was enlarged to the umbilicus. There was dulness and coarse

râles on the right side of the chest. The patient is still in the hospital and the urine still presents a 4 plus albumin. There were sinuses discharging pus in the right inguinal region and the sacrum.

There was no agreement between the Weltmann reaction and the sedimentation time in this patient.

On July 16, 1936 a colored boy (*C. V.*) chart 10, age 11 years was admitted to the hospital complaining of loss of weight, poor appetite and cough for the past two months. Previous to admission to the hospital he had a phrenic

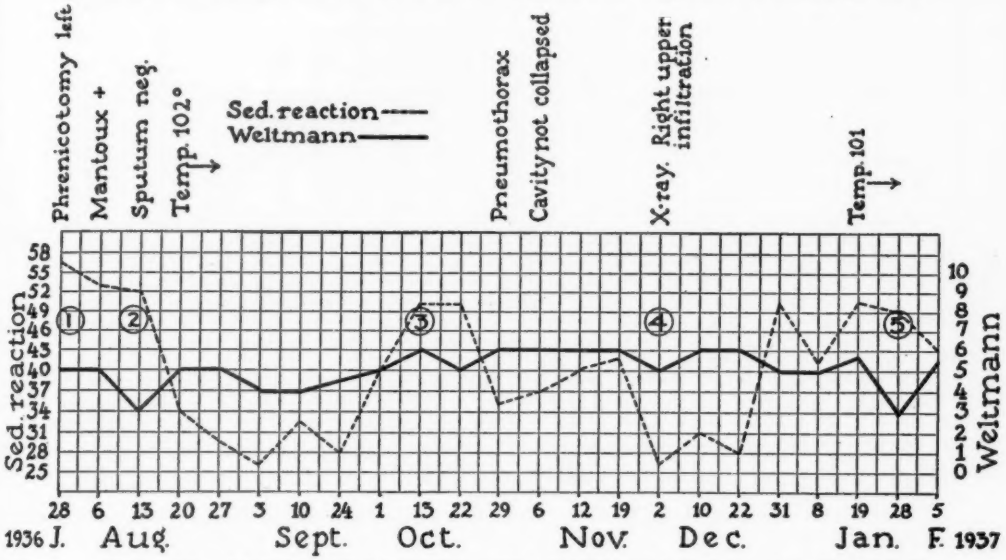

Phrenicotomy left
Mantoux +
Sputum neg.
Temp. 102°
Sed. reaction
Weltmann
Pneumothorax
Cavity not collapsed
X-ray. Right upper infiltration
Temp. 101
Sed. reaction
58 55 52 49 46 43 40 37 34 31 28 25
Weltmann
10 9 8 7 6 5 4 3 2 1 0
1 2 3 4 5
28 6 13 20 27 3 10 24 1 15 22 29 6 12 19 2 10 22 31 8 19 28 5
1936 J. Aug. Sept. Oct. Nov. Dec. Jan. F. 1937

CHART 10. Adult type of tuberculosis with bilateral involvement and cavitation left side. Negro boy eleven years of age. The sedimentation rate is always rapid although the Weltmann reaction is normal part of the time.

operation on the left side. Chart 10 shows that the coagulation band gave a slight shift to the left, as indicated by ① on the chart and the sedimentation rate was rapid. The physical examination showed râles in the left upper lobe of the lung. The sputum was negative for tubercle bacilli, and the Mantoux test was positive. His temperature went up to 102° and the Weltmann reaction gave a marked shift to the left ②, although the sedimentation rate tended to approach normal. As the patient was improving clinically, the physical examination of the chest was essentially negative. The coagulation band at this time was close to the normal zone but the sedimentation rate was rapid. The patient's temperature went up again to 102°F. and the sedimentation reaction was rapid while the Weltmann reaction went to the left. In

the latter part of October the patient received pneumothorax treatment but the cavity did not collapse. The Weltmann reaction was near the normal zone and the sedimentation rate was rapid ①. In the early part of December, 1936, the Weltmann reaction showed a slight shift to the left ②, the sedimentation reaction became closer to normal limits, but the physical findings revealed an infiltration in the upper two-thirds of the right lung. The temperature at this time was 101°. X-ray examination revealed a cavity surrounded by a thick wall and parenchymal infiltration on the right side. The diagnosis was an adult type of tuberculosis with bilateral involvement and

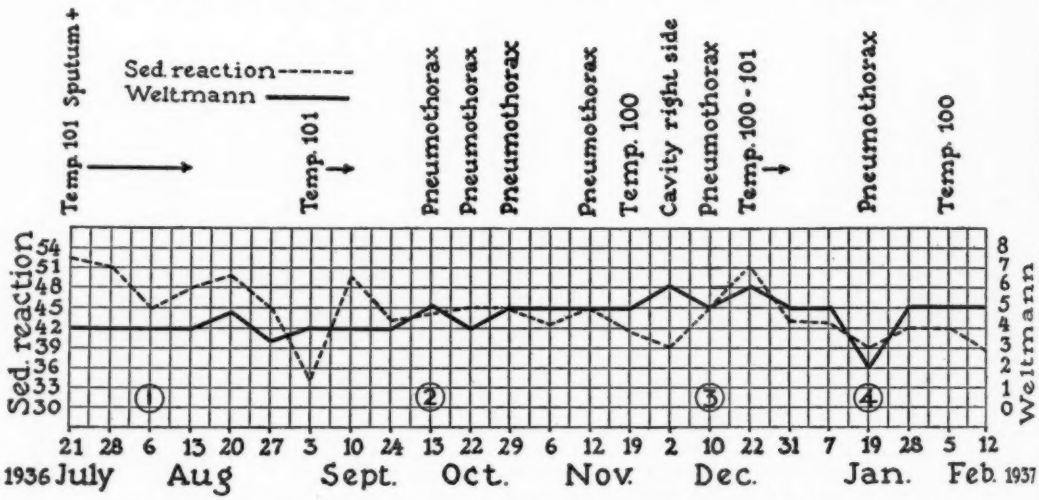

Temp. 101 Sputum +
Sed. reaction-------
Weltmann ——
Temp. 101
Pneumothorax
Pneumothorax
Pneumothorax
Pneumothorax
Temp. 100
Cavity right side
Pneumothorax
Temp. 100 - 101
Pneumothorax
Temp. 100
Sed. reaction
54 51 48 45 42 39 36 33 30
Weltmann
8 7 6 5 4 3 2 1 0
① ② ③ ④
21 28 6 13 20 27 3 10 24 13 22 29 6 12 19 2 10 22 31 7 19 28 5 12
1936 July Aug Sept. Oct. Nov. Dec. Jan. Feb. 1937

CHART 11. Pneumothorax treatment in a Mexican girl thirteen years of age who had a tuberculous involvement in both lung fields. Here the sedimentation rate is rapid and the Weltmann reaction is in the exudative zone.

cavitation on the left side. The patient showed slight improvement ④ and was transferred to the Municipal Tuberculosis Sanitarium.

There was no correlation between the Weltmann reaction and the sedimentation time in this patient.

A comparison of the Weltmann and the sedimentation reactions in a case of pneumothorax treatment is shown in chart 11.

A Mexican girl (*M. A.*), 13 years of age, was admitted to the hospital complaining of cough and loss of six pounds during the past three months. She stated that her sputum was positive for tubercle bacilli and that this examination was made by a private physician. Physical examination showed dulness and râles in both upper lobes. On admission the Weltmann reaction was to the

left as indicated by ① on the chart, and the sedimentation reaction was rapid. Temperature was 101.6°F. X-ray examination at the time revealed an infiltration in the upper two-thirds of the right and upper one-third of the left lung.

The Weltmann reaction remained to the left although the sedimentation reaction showed an approach toward normal limits. The temperature was still elevated to 101°F. and in October the patient received pneumothorax treatment on the right side. She received three inflations in October, one in November, one in December and one in January, and during this time her fever went down from 101° to 100°F. The Weltmann reaction during the patient's treatment showed a shift to the left ② ④ with two practically normal Weltmann reactions, while the sedimentation reaction was rapid. In January the Weltmann reaction gave a marked shift to the left ④ and the sedimentation reaction was slightly rapid, and the X-ray examination and physical findings revealed no cavities in the right side. The patient was subsequently transferred to the Municipal Tuberculosis Sanitarium.

There was no correlation between the Weltmann reaction and the sedimentation time in this patient.

### DAILY OBSERVATIONS ON PATIENTS WITH TUBERCULOSIS

For the following three cases, *C. K.*, *H. G.* and *F. S.*, we are indebted to Dr. W. F. Petersen who has made correlative studies on these patients in relation to the meteorograph.[4] In the three cases just mentioned we have analyzed the Weltmann reaction, the sedimentation rate, the blood pH and the carbon dioxide combining power with the clinical findings. These investigations were made daily over a period of several months.

#### *Observations on Patient C. K.*

The following is the clinical history of patient *C. K.* admitted to the Research and Educational Hospital, March 6, 1936. He was a white adult male, 48 years of age, American, and a machinist by occupation. He complained of dyspnoea, loss of 30 pounds of weight during the past two years, haemoptysis one and one-half years ago, and cough for two years. He was well until two years ago, when he had a severe cold which lasted about one month. This was accompanied by a cough and he expectorated a large amount of thick yellow sputum which at times showed blood. On several occasions he noted bright red blood. He also complained of dyspnoea which persisted on and

[4] The complete analysis of these cases appears in Petersen's book *The Patient and the Weather*, vol. IV, part 2, Edwards Bros., Ann Arbor, Mich., 1937. We wish to take this opportunity to thank Dr. W. F. Petersen for permission to reproduce here a portion of a more detailed study he has made on these patients.

off for some time. He was unable to work, but was allowed to walk around in his house. One year after the onset of these symptoms the patient was admitted to the Cook County Hospital complaining of a severe cough at night. He became tired very quickly, had lost 30 to 40 pounds during the past two years, and was 30 pounds below average weight for his height.

The past history, family history, and personal habits were not pertinent.

Blood pressure was 120/88 on admission. The chest findings showed a retraction of the infra- and supraclavicular spaces with a lagging of the left upper chest on inspiration. The tactile fremitus was slightly less on the left side posteriorly, Krönig's isthmus was decreased, and the resonance diminished over the right apex. The breath-sounds were diminished throughout except in the right base. There were fine crepitant râles posteriorly over the right apex, and the anterior chest-wall where also the vocal fremitus was increased. The heart and abdomen were essentially normal. There was a slight lumbar scoliosis to the right.

Diagnosis: Pulmonary tuberculosis in both upper lobes with cavitation in the right apex and an old pleurisy at the right base. Lumbar scoliosis. *X-ray* examination March 12, 1936, showed numerous dense, small infiltrations scattered throughout both lungs with confluence in parts. There was a suggestion of cavity formation in the right upper lobe. The findings were consistent with pulmonary tuberculosis, probably associated with a pneumonoconiosis.

Laboratory findings: Kahn and Wassermann were negative. Blood chemistry: glucose 92 mgm.; N.P.N. 30 mgm.; $CO_2$ combining power 55; albumin 3.86 per cent; globulin 2.97 per cent. Urine findings were essentially normal. Haemoglobin 13 gm.; 5,280,000 red blood cells and 9,900 white blood cells. Differential count was normal. Sputum analysis was repeatedly negative for tubercle bacilli.

The numbers on the left hand side of chart 12 indicate: *1:* Clinical progress notes; *2:* black column is tuberculin reaction, each square represents one plus reaction; *3:* Weltmann serum coagulation band; *4:* sedimentation rate; *5:* $CO_2$ combining power of the blood; *6:* pH of the blood. The circles on the chart with numbers represent different episodes discussed in the text.

On admission, December 5, the patient complained of coughing paroxysms and dyspnoea. At this time the Weltmann reaction was in tube 2 and the sedimentation rate was rapid. The pH was slightly elevated and the carbon dioxide combining power was low. There followed a slight increase in the coagulation band to tube 4 for a few days as indicated by episode ①, and during this time the sedimentation rate fluctuated from a slight increase to a markedly increased reaction. The patient complained of dyspnoea in the evening with some wheezing. The pH rose to 7.48 and the carbon dioxide combining power was slightly elevated ①. For a few days after December 10 the dyspnoea was less marked, the cough dry and the Weltmann reaction was

slightly elevated to normal. The sedimentation rate was still rapid. At this time the carbon dioxide combining power dropped to 47 and the pH went up to 7.53. There was a period during which the Weltmann reaction dropped again to the 4th tube in the exudative zone. The sedimentation reaction became rapid. During this interval the patient complained of coughing spasms especially at night with dyspnoea, tired and drowsy feeling, the pH and the carbon dioxide combining power went down. From December 20 to 24 there was a marked drop in the Weltmann reaction to the zero line ⑨ and instead of the sedimentation reaction persisting in the rapid zone, it declined toward the normal zone ⑨. The carbon dioxide combining power dropped to 48 and the pH went down to 7.38 ⑨. At this time the patient complained of pain in the right intercostal space with coughing spells at night. For the remainder of the month of December, 1936, the Weltmann reaction went up to tube 4, still in the exudative zone but not as marked as in the preceding week. The sedimentation rate became rapid again. At this time the patient complained of dyspnoea and wheezing, the carbon dioxide combining power was 53 and the pH went down to 7.37 ⑨.

Again we had in the first week of January, 1937, a disagreement between the Weltmann reaction and the sedimentation rate, and an agreement between the Weltmann reaction, the carbon dioxide combining power and the pH. Between January 4 and January 10, the Weltmann reaction was zero and then it went up to tube 3, later to zero, and again rose to tube 3. During this entire period the Weltmann reaction was definitely in the exudative zone ⑨. The sedimentation rate, however, went to normal ⑨. The pH was slightly elevated, the carbon dioxide combining power went down. We see here a correlation of the blood pH with the Weltmann coagulation band, namely, that, as a rule, if the Weltmann reaction rises toward normal, the blood pH goes down toward the acid side, and conversely, as the blood pH rises toward the alkaline side, the coagulation band becomes diminished. The carbon dioxide combining power and the pH give divergent findings, as the former drops the pH goes up ⑨. The patient at this time complained of severe coughing and dyspnoea. Another episode occurred between January 11 and 15. The Weltmann reaction dropped from tube 4 to tube 1 ⑨, indicating that the process was still in the exudative stage. The sedimentation rate was slightly rapid, the carbon dioxide combining power dropped and there was a slight elevation of the pH ⑨.

The patient presented orthopnoea, dyspnoea and a severe cough. He gradually improved clinically and was feeling better part of the month of January. During this time the Weltmann reaction fluctuated from the exudative zone to the normal and slightly above the normal zone, in tube 7 ⑨. During this time the sedimentation rate was rapid ⑨ except on January 23, when it became normal as the Weltmann reaction was slightly increased to

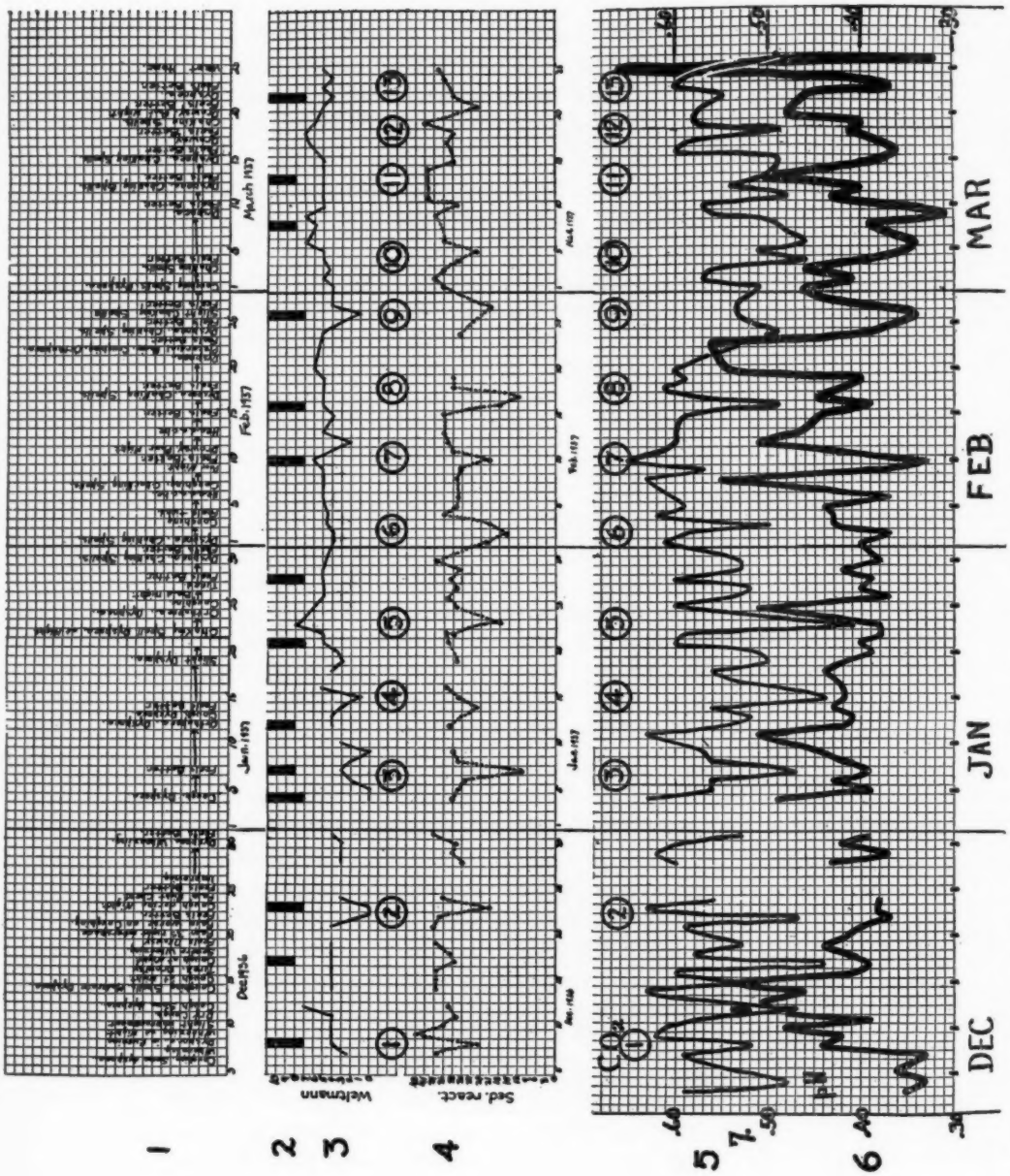



CHART 12. Patient *C. K.*, forty-eight year old white male. Pulmonary tuberculosis in both upper lobes with cavitation right apex. Correlation of the (1) clinical findings, (2) tuberculin reaction, (3) Weltmann reaction, (4) sedimentation rate, (5) $CO_2$, and (6) pH.

the right. The carbon dioxide combining power dropped considerably and there was a marked elevation of the pH. ⑤. Clinically there were attacks of dyspnoea and the patient complained of feeling tired and had some choking spells.

In the early part of February, 1937, the Weltmann reaction dropped to tube 4 ⑥ and the patient had severe dyspnoeic and choking spells and was coughing. The sedimentation rate, however, approached normal ⑥ and the pH started to go up and the carbon dioxide combining power was low ⑥. For the first ten days in February, 1937, there was a slight rise in the Weltmann reaction to normal ⑦ and at this time, although the patient showed very little clinical improvement, he did not complain of distress symptoms as he did during the previous week. The sedimentation rate fluctuated in the rapid zone ⑦ and then on February 12 the Weltmann reaction dropped to tube 2. The sedimentation rate went up and at this the patient complained of headache. There was a drop in the pH to 7.33 and the carbon dioxide combining power rose to 65 ⑦.

From February 16 to 22, the Weltmann reaction still remained in the exudative zone ⑧, the patient was dyspnoeic, the sedimentation rate was slightly rapid ⑧, the pH went up to 7.56 and then there was a sudden drop in the carbon dioxide combining power ⑧. On February 26 the Weltmann reaction shifted to the left in tube 1 ⑨. The sedimentation rate instead of being rapid at this time approached normal ⑨. The pH was down and the carbon dioxide combining power was slightly elevated ⑨. The patient complained of severe precordial pain with dyspnoea, orthopnoea and coughing spasms. There was a slight improvement in the first week of March, 1937, when the Weltmann reaction gradually came up to the normal zone ⑩. The sedimentation rate was still rapid ⑩ and the patient stated he felt better, and the choking spells were not as severe as they were in the last week. During this time the carbon dioxide combining power and the pH dropped slightly but rapidly returned to the preceding level ⑩.

During the week of March 10 to 15 the Weltmann reaction dropped toward the exudative zone ⑪ in tube 5, the sedimentation rate became rapid ⑪. The carbon dioxide combining power rose and the pH dropped ⑪ and the patient complained of attacks of dyspnoea and choking spasms. From the 15th to the 20th of March there was a slight elevation of the Weltmann reaction ⑫ in the normal zone, the sedimentation reaction continued to be rapid ⑫. The patient stated he was feeling better, but somewhat drowsy. The carbon dioxide combining power was diminished, but there was an elevation of the pH ⑫.

For the remainder of March, 1937, before the patient left for home, the Weltmann reaction dropped to the 3rd and 4th tubes indicating that the anatomical changes were still reflected in the exudative zone ⑬, the pH was

apex. Correlation of the (1) clinical findings, (2) tuberculin reaction, (3) Weltmann reaction, (4) sedimentation rate, (5) $CO_2$, and (6) pH.

rather high at this time (7.66) and suddenly dropped to 7.33 ⊛, the carbon dioxide combining power remained high. The sedimentation time remained rapid ⊛. The patient, although he stated he felt better, still had attacks of dyspnoea and some choking spells.

*Tuberculin skin reactions:* Through the kindness of Dr. John Howe who has made daily tuberculin skin tests using the von Groer technique on the patients studied, we have inserted these results on chart 12. The tuberculin test is represented by a 3 or 4 plus reaction. The solid black lines indicate tuberculin, and each square represents a plus reaction. When the extensive tuberculin reactions are compared with the Weltmann coagulation band it is noted that invariably when the tuberculin reaction was 3 or 4 plus the Weltmann reaction was in the exudative zone. Such a definite correlation did not exist between the tuberculin reaction and the sedimentation rate. The analysis of the correlation of the marked skin tuberculin test with the Weltmann reaction as it swings in the exudative zone is merely a reflection of the anatomical processes that take place in the human organism. When the anatomical changes indicating exudation occur, as is reflected in the coagulation band, the patient invariably gives a 3 or 4 plus tuberculin test. The skin blood vessels become more permeable and the response to the tuberculin reaction is more pronounced.

### *Observations on Patient H. G.*

A 38 year old, white male, American born, was admitted to the Research and Educational Hospital on December 4, 1936. He was a laborer by occupation. Previous to admission to the Research and Educational Hospital, he was at the Cook County Tuberculosis Hospital from October 1 to December 4, 1936. He complained of pain in the right chest and night sweats for eight weeks, and loss of 6 pounds since the onset of symptoms; cough and expectoration for eight weeks, and loss of appetite.

He was well until eight weeks before admission to the hospital when he began to cough and bring up sputum which was blood-streaked at times. He had night sweats and sharp pain in the chest, particularly on coughing. He applied at the Cook County Hospital for examination and X-ray revealed a tuberculous lesion of the lung.

The past history was essentially negative except that he had had measles, mumps and scarlet fever. He denied syphilis. He did not use alcohol, and smoked only 3 or 4 cigarettes a day.

Mother, sisters and one brother were living and well. His father died of "pleural pneumonia" at the age of 72.

The patient stated that he was in good health until October, 1933 when he had an attack of pleurisy in the left chest. He was at home for two months and under the care of a doctor. His weight went down from 135 pounds to

95 pounds at this time. He recovered from this illness and returned to work as a laborer. For the succeeding three years he continued at this occupation, but he fatigued readily.

About September, 1936, the patient contracted a "chest cold" with a sharp pain in the right chest, exaggerated on coughing and on inspiration. This was followed by a productive cough, and on many occasions blood-streaked sputum was seen. These symptoms persisted until he was admitted to the Cook County Hospital.

On physical examination, the patient was a fairly well developed, rather slender white male. Blood pressure was 130/80; respirations 18; pulse 84; temperature 98.6°F. In the left axilla there was a subcutaneous mass about the size of a golf ball which was encapsulated, soft and fluctuant, with a small amount of white pus expressed from an opening in its centre. There was diminished resonance over the right apex with moist râles persistent after coughing. The heart and the abdominal organs were essentially negative.

Impression: Right apical tuberculosis with a cold abscess in the left axilla.

Laboratory findings: Haemoglobin 11 gm.; red blood cells 5,200,000; white blood cells 12,500. Differential count: lymphocytes 35 per cent; monocytes 4 per cent; polymorphonuclear leucocytes 60 per cent; eosinophiles 1 per cent. Serum albumin 3.74; serum globulin 3.6; glucose 85 mgm.; N.P.N. 29; carbon dioxide combining power 57; Kahn test negative.

Fluoroscopic examination and an X-ray film showed an irregular density over the upper part of the right upper lobe with suspicion of beginning cavity formation. These findings are consistent with pulmonary tuberculosis.

During the entire stay in the hospital, the patient was afebrile with exception of three days when his temperature reached the maximum of 100°F. The pulse fluctuated from 80 to 100; respirations from 12 to 20.

The numbers on the left-hand side of chart 13 indicate: *1:* Clinical progress notes; *2:* black column tuberculin reaction of which each square represents one plus; *3:* Weltmann serum coagulation reaction; *4:* sedimentation rate; *5:* carbon dioxide combining power of the blood; *6:* blood pH. Circles with number on the chart represent different episodes described in the text.

On admission to the hospital the Weltmann reaction was in tube 2½ which is in the exudative zone ①. The sedimentation rate was rapid ①. At this time the carbon dioxide combining power was normal, but the pH was low on the acid side ①. He complained of a cough and a tight feeling in his chest. There was a slight improvement for a few days after that until December 10, 1936. During this time the Weltmann reaction moved slightly toward the normal zone and the sedimentation reaction was diminished ②. The hydrogen ion concentration was elevated and the carbon dioxide combining power dropped ②. Then on December 12, the patient complained of a dry cough

but the Weltmann reaction went to normal ⊙. The sedimentation rate dropped, and the hydrogen ion concentration of the blood approached the acid side ⊙. Then for several weeks after that the Weltmann reaction remained more or less uniform in tube 4 ⊙ which indicated a slight exudative reaction. The sedimentation rate fluctuated in the high zone ⊙ and the carbon dioxide combining power of the blood dropped, while there was a rise in the pH ⊙. During this period the patient complained of coughing particularly at night, and some dyspnoea. The Weltmann reaction dropped to the zero tube ⊙ indicating a marked exudative process, and at the same time the sedimentation rate approached normal ⊙. The carbon dioxide combining power dropped considerably and the pH showed a slight rise ⊙. Clinically the patient complained of severe chest pains, vomited food, and had chills and night sweats. At this time the Weltmann reaction correlated with the anatomical changes taking place in the patient, whereas the sedimentation reaction indicated improvement. During the interval between December 24 and January 4, the patient showed a slight improvement, the Weltmann reaction returned to normal, and the sedimentation rate was slightly rapid. Then on January 4, 1937 the patient complained of marked dyspnoea and cough. X-ray examination showed that the cavity had enlarged and that there was infiltration in the lung. The Weltmann reaction was zero ⊙ and the sedimentation rate was slightly rapid. The carbon dioxide combining power began to rise at this point, and the pH was slightly elevated. Then in the following few days the patient felt some slight improvement, the Weltmann reaction rose slightly but still remained in the exudative zone ⊙ while the sedimentation reaction returned to normal. At this time the pH dropped and the carbon dioxide combining power rose ⊙. He remained stationary for a short time during this period and on January 12 he complained of coughing paroxysms which lasted several days. At this time the Weltmann reaction dropped to the first tube which indicated a marked exudative change ⊙, and the sedimentation reaction approached the normal zone. The pH rose and the carbon dioxide combining power dropped ⊙. From January 20 to 24 the patient showed slight improvement and he gained one pound in weight. At this time the Weltmann reaction began to approach normal ⊙, and there was agreement in the sedimentation rate which was also normal ⊙. The carbon dioxide combining power went up to 63 and the pH was 7.48 ⊙. The patient developed diarrhoea on January 24 and complained of poor appetite, nervousness and inability to sleep, which lasted for two days. At this point the Weltmann reaction dropped to the second tube ⊙, which indicated exudation, and there was a rise in the sedimentation rate ⊙. At this time the pH was elevated and the carbon dioxide combining power diminished ⊙. Then there was a gradual clinical improvement and the patient stated he felt better. The coughing was not so severe and he gained some weight. This lasted for about

two weeks, and later the patient complained of abdominal cramps. The Weltmann reaction dropped in the exudative zone ⑨ and the sedimentation fluctuated with rapid rates ⑩. Apparently there is no correlation between the sedimentation rate and the Weltmann reaction as compared with the clinical findings.

For example, on February 9, the Weltmann reaction was in tube 2 and the sedimentation rate normal, and at this time the pH dropped and the carbon dioxide combining power diminished. On February 10 there was a slight improvement in the clinical status of the patient and the Weltmann reaction went up to tube 4 and there was a sudden rise in the sedimentation reaction ⑪. The pH dropped and the carbon dioxide combining power went up ⑫. The X-ray film at this time showed the cavity somewhat smaller and infiltration of the lung diminished. On February 12 the patient complained of severe coughing in the morning and at this time the Weltmann reaction dropped to tube 3 ⑬ and the sedimentation rate began to approach the normal zone. The pH and the carbon dioxide combining power were elevated ⑭. For a week or so following this episode, the patient felt better and gained at one time three and one-half pounds in weight and the following week two and one-half pounds in weight. The Weltmann reaction rose toward the normal zone ⑮. The sedimentation rate still remained rapid ⑯, the pH dropped and the carbon dioxide combining power rose ⑰. Corresponding with fluctuations that occur in the Weltmann reaction are the peaks ⑱, that are demonstrated in the blood pH.

On February 24 and 25 the patient complained of a head cold, nasal discharge and sinusitis. The Weltmann reaction dropped to the 4th ⑲ tube and the sedimentation rate was slightly rapid ⑳ while the pH and carbon dioxide combining power were slightly elevated ㉑. For the following week the patient gained two pounds in weight, stated that he felt better, and was improving, although the rise in the coagulation band was very slight ㉒, whereas the sedimentation rate approached the normal zone ㉓. This improvement continued until March 9 when the Weltmann reaction was slightly above the normal zone ㉔, and the patient had gained some in weight. The sedimentation rate fluctuated from the normal to the abnormal zone ㉕. The Weltmann reaction remained constant. Then on March 11 the patient complained of pain and stiff joints. The Weltmann reaction suddenly dropped from the 8th tube which is above the normal zone to the 5th which is in the exudative zone ㉖. The sedimentation rate was almost normal. The carbon dioxide combining power rose and the pH dropped ㉗. This lasted for almost a week during which time the patient lost one and one-half pounds in weight. The Weltmann reaction still remained in the exudative zone ㉘, and the sedimentation rate was slightly rapid ㉙; the carbon dioxide combining power dropped, and the pH went up ㉚. From about March 15 to 24, the clinical condition

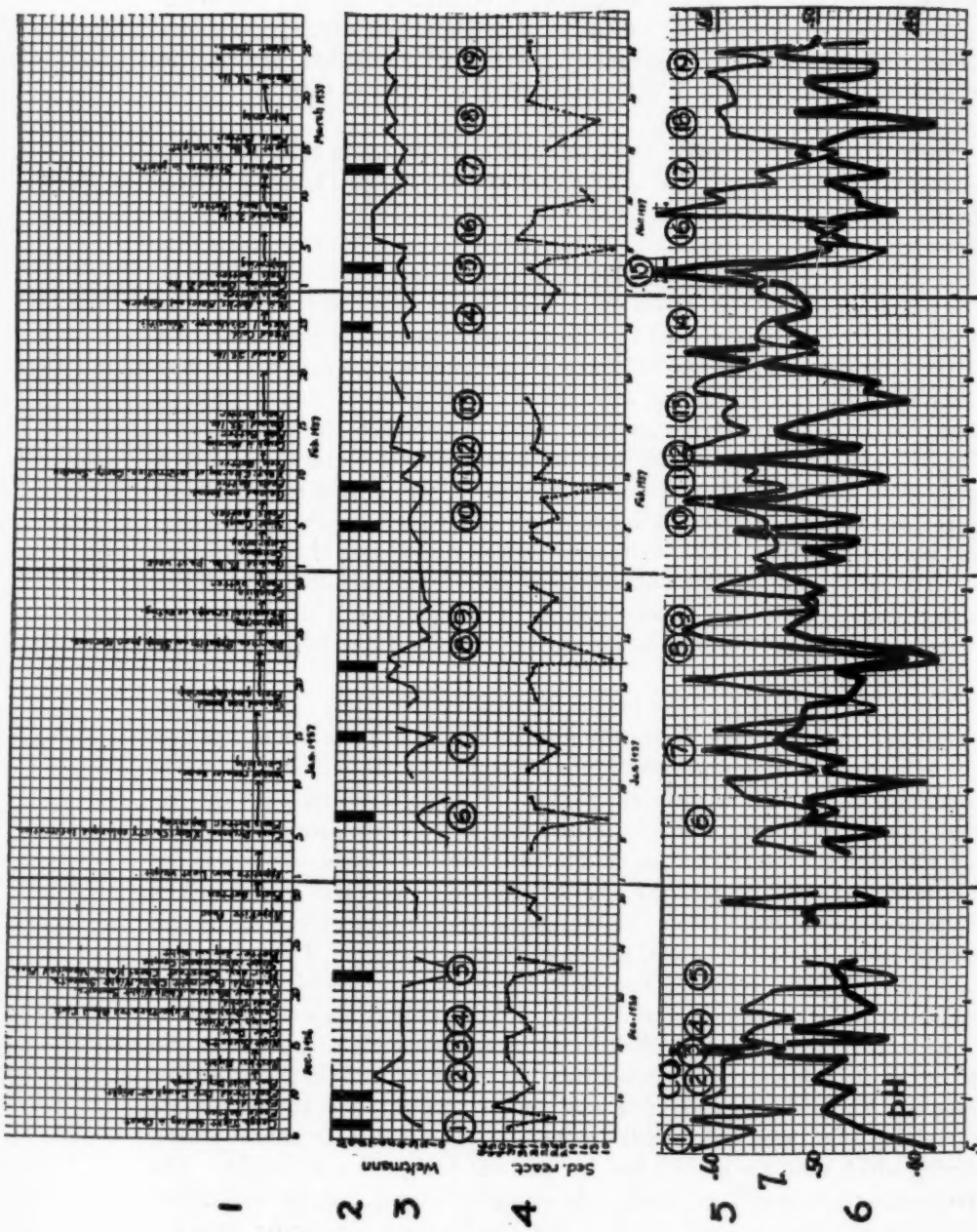



CHART 13. Patient *H. G.*, thirty-eight year old white male. Right apical tuberculosis with cavity formation and a cold abscess left axilla. Correlation of the (1) clinical findings, (2) tuberculin reaction, (3) Weltmann reaction, (4) sedimentation rate, (5) $CO_2$,

showed some signs of improvement, and although the patient gained three and one-half pounds in weight during this time the Weltmann reaction was within the normal zone, the sedimentation rate was rapid, the pH fluctuated to the lower ranges and the carbon dioxide combining power rose. On March 25 the patient insisted upon returning home and we were unable to follow the patient from this time on.

In chart 13 the tuberculin skin tests are indicated by the black column 2, each square representing a plus mark indicating the degree of reaction. In chart 13 and in the previous chart 12, the more extensive tuberculin skin reactions almost parallel the Weltmann coagulation band. Here, too, as the Weltmann reaction is in the exudative zone, the degree of the tuberculin skin reaction is more extensive. In this chart as in the preceding one, there is not at all times a correlation between the tuberculin reaction and the sedimentation rate, as there is between the tuberculin skin tests and the Weltmann reaction.

### *Observations on Patient F. S.*

A 51 year old, Mexican male was admitted to the Research and Educational Hospital, November 7, 1935, complaining of severe colds every winter lasting about ten days. In May, 1934 he developed pain in the right chest which was aggravated on deep breathing, and fever. He was diagnosed as pneumonia at that time. For the following four months he had a cough and pain in the chest, and he became progressively weaker, and began to lose weight. In October, 1934, his condition was diagnosed as tuberculosis.

He was kept in bed for 4 months, and during this time the temperature was elevated to 103°F. On September 17, 1935 he had haemoptysis, followed by blood-streaked sputum which lasted for almost eight hours. At the time of admission to our institution he complained of pleurisy and a productive cough.

He had an attack of catarrhal jaundice which was characterized by nausea and vomiting, jaundice of the skin and the sclera. This lasted 5 to 6 weeks. He had "rheumatism of the legs" at the age of 7 years; also gonorrhoea 30 years ago.

Father and mother are dead, age and cause unknown. He had no knowledge of whereabouts of brother and sister, but believed there was no history of tuberculosis or contact tuberculosis in his family.

The patient was a moderately emaciated Mexican male with prominent ribs. There was impairment of the percussion note on the right posterior chest-wall with increased tactile fremitus and increased transmission of spoken and whispered voice in this region. In the right supraclavicular region, the percussion note was hyperresonant, with amphoric breathing and whispered pectoriloquy and râles in this region. The left chest-wall was essentially normal.

CHART 13. Patient *H. G.*, thirty-eight year old white male. Right apical tuberculosis with cavity formation and a cold abscess left axilla. Correlation of the (1) clinical findings, (2) tuberculin reaction, (3) Weltmann reaction, (4) sedimentation rate, (5) $CO_2$.

Examination of the abdominal organs was essentially negative except for a reducible right indirect inguinal hernia. Blood pressure was 106/98, pulse 90. Examination of the skin, reflexes and the extremities was essentially negative.

Impression: Pulmonary tuberculosis with cavities at right apex and infiltration of right upper and lower lobes. Indirect inguinal hernia. The subsequent clinical progress of this patient is recorded under clinical notes on chart 14.

Laboratory findings: Kahn 3 plus; Wassermann, anticomplimentary. Urine negative. Blood: 4,700,000 erythrocytes; 15,000 leucocytes. Sputum always positive for tubercle bacilli. Temperature fluctuated from subnormal to 101°F. Pulse 80 to 120.

Fluoroscopic examination and a film showed numerous infiltrations in the right lung and left lower lobe, markedly dense over right upper lobe with a localized radiolucent shadow within it. The right diaphragm showed evidences of adhesions. These findings are consistent with pulmonary tuberculosis with cavitation and pleural complications.

The patient died August 10, 1936. *Autopsy findings:* (*1*) chronic fibroulcerative caseous pulmonary tuberculosis; (*2*) dense bilateral pleural adhesions; (*3*) brown atrophy of the myocardium; (*4*) tuberculosis of tracheobronchial, celiac and mesenteric lymph nodes; (*5*) atrophy of the liver; (*6*) moderate atherosclerosis of the aorta and coronary arteries; and (*7*) emaciation.

The numbers in the right side of chart 14 denote: *1:* Clinical progress notes; *2:* cholesterol; *3:* carbon dioxide combining power of the blood; *4:* blood pH; *5:* Weltmann serum coagulation reaction. The circles with numbers on the chart represent different episodes described in the text.

On admission, in November, 1935, the patient complained of a cough and weakness with dyspnoea. During this time the cholesterol dropped from 188 to 144 mgm. ①. There was an elevation in the carbon dioxide combining power and a drop in the pH ①. The Weltmann reaction at this time was in the exudative zone ①, in fact the coagulation band persisted in this slight shift to the left for the remainder of November, 1935 and the first part of December, 1935.

A second episode occurred when the pH dropped to 7.46 ② and the carbon dioxide combining power rose to 58, the cholesterol was 150 mgm. ②. The patient still complained of cough and weakness. There was a correlation of the blood pH with the Weltmann reaction ② during the month of December, 1935. The swing of the pH was opposite to that of the Weltmann reaction. This factor we shall point out in chart 15, when we compare on a larger scale the blood pH with the Weltmann reaction.

A third striking episode occurred in January, 1936. The patient complained of a severe cough and the cholesterol dropped from a high level of 174 to the low level of 134 mgm. ③. The fluctuations of the carbon dioxide combining power almost mirrored the swing of the cholesterol, whereas the blood

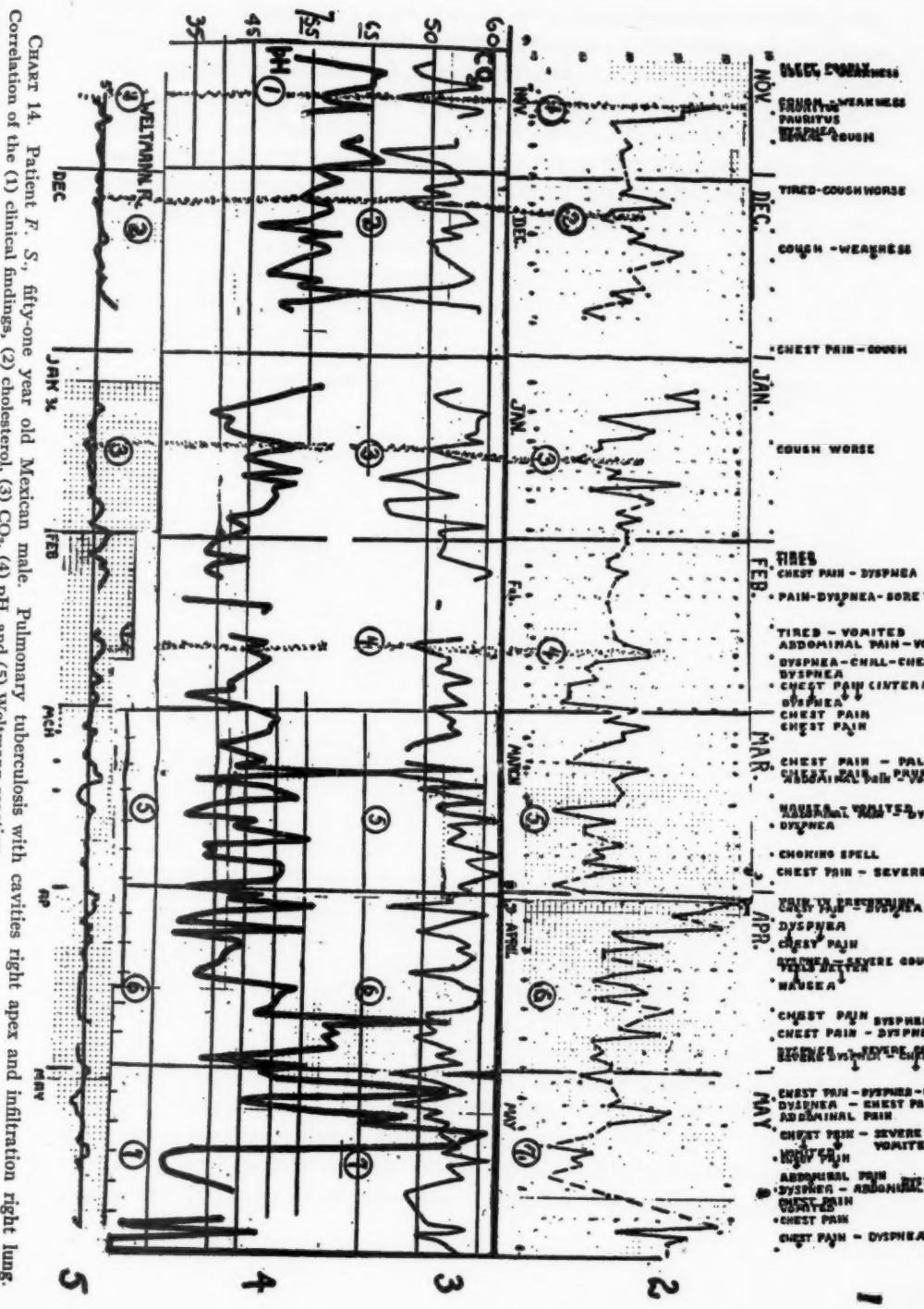



CHART 14. Patient *F. S.*, fifty-one year old Mexican male. Pulmonary tuberculosis with cavities right apex and infiltration right lung. Correlation of the (1) clinical findings, (2) cholesterol, (3) $CO_2$, (4) pH, and (5) Weltmann reaction.

pH ⊙ and the Weltmann reaction simulated one another insofar as the Weltmann reaction reflected the opposite swing of the blood pH ⊙. There was a slight improvement in the clinical condition of the patient for the most part of February, 1936, although the patient complained of chest pains and dyspnoea. There was a slight elevation in the blood cholesterol ⊙ and the carbon dioxide combining power, but the pH dropped ⊙ while the coagulation band was within the normal zone ⊙. In March, 1936 there was an exaggeration of the symptoms complained of by the patient in the previous months, and between the time of his chest and abdominal pains and the periods of remission of these complications, the cholesterol level swung from a normal range to a low level ⊙, while the carbon dioxide combining power remained elevated ⊙. There was a fluctuation in the blood hydrogen ion concentration

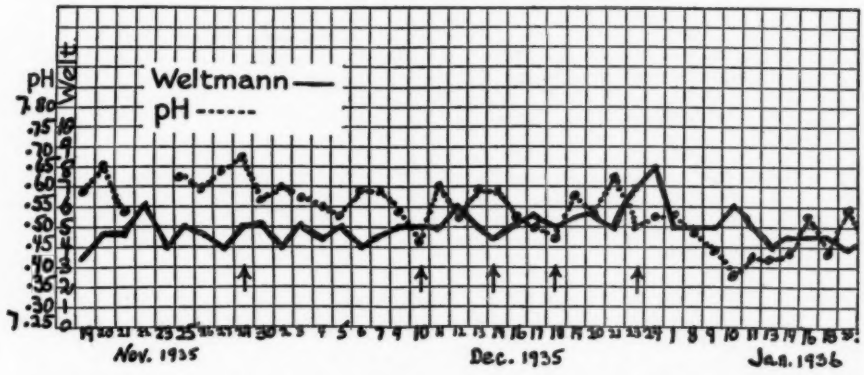



CHART 15. Comparison of the blood pH and the Weltmann reaction. Patient *F. S.* With a rise in the pH the coagulation band decreases and with a drop in the pH the coagulation band increases.

from a low to a high level during this time, with a corresponding fluctuation of the Weltmann reaction from the normal to the exudative zones ⊙. In April the symptoms became more aggravated, the dyspnoea and the chest pains were more intense, the cough more troublesome, and the patient complained of precordial pain. This was manifested by a fluctuation of the cholesterol from the normal to the low level ⊙. The carbon dioxide combining power remained elevated. The blood pH went from the acid to the alkaline zone ⊙. The coagulation band remained in the exudative side ⊙. Then in May, 1936 there was a continuation of the findings as described in the previous months in a degree which was more pronounced, the blood cholesterol dropped to a lower level ⊙, there was a rise in the carbon dioxide combining power and a marked elevation of the blood pH to the alkaline zone ⊙, with a sudden drop to the acid side. The Weltmann curve went to the exudative zone when

there was an elevation of the pH. As the pH dropped to the acid side the Weltmann reaction approached a normal level ⊙. It dropped again to the exudative zone shortly before the patient expired.

### COMPARISON OF THE BLOOD pH WITH THE WELTMANN REACTION

Chart 15 is an enlargement of the portion of chart 14 that concerns itself with the hydrogen ion concentration of the blood and the Weltmann serum coagulation reaction. It is obvious from this chart that, as the blood pH goes down toward the acid side, the Weltmann coagulation band is elevated to the right, the productive zone. Conversely, when the blood pH swings toward the alkaline side, the coagulation band drops toward the exudative zone. These swings in the opposite direction of the blood pH and the Weltmann reaction are indicated on the chart by arrows. There is no relationship between these reactions on the basis of the explanation of their mechanisms. Certainly the blood pH does not directly affect the serum coagulation reaction. However, the biochemical test does show this interesting correlation. This is not only noticed in chart 15 but in charts 12, 13 and 14 where the comparative studies include blood pH and the Weltmann reaction.

### DISCUSSION

It is the concensus of the European investigators who have worked with the Weltmann serum coagulation reaction in tuberculosis that this test is an extremely valuable aid in the diagnosis and prognosis of this disease. Weltmann in his first report had indicated that this reaction is one that distinguishes exudative inflammatory reactions from fibrotic changes. He believed that the blood in these conditions reflects the anatomical changes that take place in the body. There is no doubt that this opinion of Weltmann is correct, because it has been corroborated by investigators not only in the field of tuberculosis, but in practically all diseases which have been studied. For example, Makitra and Tyndel (5) have determined the Weltmann reaction in 200 patients with tuberculosis and their results indicated that in incipient cases of exudative tuberculosis the coagulation band gave more reliable diagnostic results than did the sedimentation speed of the erythrocytes. These authors believed that in chronic tuberculosis the Weltmann reaction has prognostic value.

We have compared the sedimentation rate with the Weltmann reaction because the former has been used very extensively, particularly in tuber-

culosis as a diagnostic aid as well as a prognostic guide. The sedimentation rate responds readily to the slightest alterations that occur in the body and is less stable than the Weltmann reaction. Although the exact mechanism of this test is not known, the fact remains that a rapid sedimentation rate occurs not only in destructive changes in the organs, but also in diseases associated with repair, and in certain physiological conditions. For example, in normal pregnancy, the sedimentation rate is more rapid than normal, but the Weltmann reaction gives a normal reading. Also in diseases associated with inflammatory changes, such as acute rheumatic polyarthritis, the sedimentation rate is rapid, and the Weltmann reaction gives a shift to the left. This may be contrasted with disease conditions associated with fibrosis, such as lymphogranuloma inguinale. This latter condition gives a rapid sedimentation rate, but the Weltmann reaction is usually normal or to the right and is indicative of fibrotic changes. Therefore, if one is to follow the sedimentation reaction alone, one cannot definitely determine by this test if the fluctuation that occurs in the speed of sedimentation of the erythrocytes indicates exudative, destructive, inflammatory or reparative changes. Jores and Strutz (6) have shown that the sedimentation rate has a rhythmic diurnal variation. They observed that in normal individuals the sedimentation rate may fluctuate within the 24-hour period from normal to abnormal values. The same holds true for studies made in disease conditions. In further studies, these authors found that the examination of different patients on the same day resulted in similar curves, whereas the examination of the same patients on different days resulted in different curves. These investigators believed that the sedimentation value must be interpreted cautiously for the reason that in normal individuals one may at certain times obtain abnormal results. When the blood is examined in the morning the sedimentation rate is rapid, and, when repeated again in the evening on the same patient, a normal result may be obtained. These differences that are found in the sedimentation rate do not occur in the Weltmann test.

It makes little difference if the blood is drawn in the morning or in the evening on the same patient as far as the serum coagulation reaction is concerned, because the amount of the precipitation is not as unstable as the speed of sedimentation of erythrocytes. We have examined normal as well as diseased subjects, making several tests each day on the same individuals, and the Weltmann reaction is the same if the clinical condition is stable in these cases.

Voigtländer (7) in his studies on 400 patients in a tuberculosis sanatorium believed that the Weltmann serum coagulation reaction is helpful in the diagnosis and prognosis of tuberculosis. He stated that this reaction enables the clinician to arrive at a decision as to whether the tuberculous process is of the exudative or of the fibrotic type. This investigator, as well as Weltmann, has compared the serum coagulation band of patients with febrile processes and with those who had artificially induced fever. Voigtländer showed that when fever was artificially induced the coagulation band was normal; whereas, in febrile conditions, if the coagulation band gave a shift to the left it indicated an inflammatory change, such as an exudation that occurs in pulmonary tuberculosis, pleurisy with effusion, or a suppurative process. This factor is important because in attempting to determine the nature of a febrile condition, if the Weltmann coagulation band gives a normal reaction or a shift to the right, an exudative process is ruled out. Voigtländer in his report indicated that the coagulation band shows no deviation to the left without an inflammatory or an exudative process, and that the degree of deviation runs parallel with the severity of the process. One may therefore use the Weltmann reaction as a quantitative means of determining the degree of anatomical changes that occur. As the inflammatory process improves the coagulation band returns to normal. Then as repair takes place with deposit of fibrous tissue, the Weltmann reaction gives a deviation to the right. This is seen in conditions such as cirrhosis of the liver, as well as in fibrotic forms of tuberculosis. In this manner one might establish an index as to tissue damage and tissue repair using the Weltmann serum coagulation reaction as a reflection of the anatomical changes occurring in the body. This is true providing only one or the other change takes place. It is well known that in a tuberculous patient inflammatory processes and cavity formation with exudative changes may occur, while at the same time fibrous tissue reaction takes place in the same lung or in the other lung. In other words, pulmonary disorders in which exudative and fibrotic processes concur cannot always be clarified by the Weltmann reaction. Here, the Weltmann coagulation band will approach the normal, because the two opposite reactions, exudative and fibrotic, take place. This can be demonstrated by taking the blood from a pneumonia patient which gives a zero Weltmann reaction and mixing it in a test tube with the blood of a patient with cirrhosis of the liver which gives a coagulation band of 8 or 9. This will result in a coagulation band of 3

or 4. Hence, if exudative and fibrotic changes occur in the patient at the same time, a similar reaction will be obtained as was just mentioned.

Dissmann (8) performed the Weltmann reaction on 274 tuberculous patients and compared it with results obtained in nonspecific pulmonary diseases, and in normal persons. He observed a shortening of the coagulation band in nearly all cases of exudative inflammatory disturbances, and the extent of the shortening usually corresponded to the severity of the inflammation. Fibrocaseous tuberculosis during the interval of disease and fibroulcerative tuberculosis frequently gave a normal coagulation band. A shift to the right of the coagulation band was noticed almost exclusively in purely productive tuberculosis, in the closed cavity and healing types of tuberculosis. The author believed that the sedimentation rate and the coagulation band did not always run parallel. He was of the opinion that the Weltmann serum coagulation band is of more value for the estimation of the inflammatory process than is the sedimentation rate.

Other investigators, such as Nizegorodcew (9) who examined 150 cases of tuberculosis with the Weltmann reaction, report similar findings. Alonso (10) compared the Weltmann reaction with the sedimentation reaction and the leucocyte count, and believed that all three tests are good prognostic aids. Barsotelli and Poggioni (11) studied the Weltmann reaction in 34 patients who were treated by artificial pneumothorax. Of this number, 6 received bilateral pneumothorax. They concluded that when the Weltmann reaction gave a shift to the right it paralleled the clinical improvement of the patient, whereas, when the coagulation band gave a shift to the left it was accompanied by complications in the pleural cavity. Their conclusions were that the Weltmann reaction parallels the clinical course of the condition.

Concerning the rôle of the Takata-Ara reaction in tuberculosis, Schneiderbaur (12) is of the opinion that this reaction does not act as a guide to the activity in pulmonary tuberculosis, and that the Weltmann reaction is a more reliable index. Friedmann (13) is of the opinion that the Weltmann reaction is of definite value in establishing the pathological anatomical changes as well as a prognostic index in pulmonary tuberculosis. Scherleitner (14) analyzed 134 cases and indicated the value of the Weltmann reaction in distinguishing exudative from productive processes. In her report she concluded that when a shortening of the coagulation band was obtained the prognosis in tuberculosis was poor, as compared with a prolonged coagulation band or a shift to the right, in

which the prognosis was more favorable. In tuberculous meningitis, and in miliary tuberculosis, the coagulation band gave an extreme shift to the left; in bone tuberculosis the coagulation band was to the right.

### ANALYSIS OF OUR CASES

The observations made on the cases we have reported substantiate the results of the investigators quoted above. In chart 2 we have recorded the sedimentation rate and the Weltmann reaction in a group of patients with far advanced pulmonary tuberculosis. A perusal of the chart shows that most of the cases gave a rapid sedimentation rate. The Weltmann reaction went from the extreme degree of exudation as manifested in the extreme shift to the left, to a shift to the right in which group the patients showed clinical improvement. These far advanced cases varied from those that showed exudative and anatomical changes with cavity formation to those that had fibroulcerative tuberculosis with clinical improvement. In the group of cases that were very sick, and those that died, there often was an agreement between the two reactions: the sedimentation reaction was rapid, and the Weltmann reaction gave an extreme shift to the left in the exudative zone. In the group of far advanced cases that improved and some that were discharged from the institution as arrested cases, the Weltmann reaction gave a shift to the right which indicated fibroid changes, but the sedimentation reaction still remained rapid.

In chart 3 we have compared the moderately advanced cases of tuberculosis with the sedimentation rate and the Weltmann reaction. The same analysis holds true for this group of cases as was mentioned above for the group of far advanced cases. Here too, there was no correlation between the sedimentation rate and the Weltmann reaction.

All of the patients who were clinically diagnosed incipient pulmonary tuberculosis were ultimately released from the institution as improved healed cases. This group is represented in chart 4. All of the patients gave a negative sputum, the Weltmann reaction was normal, and some gave a shift to the right; whereas the sedimentation rate was rapid.

In our three main groups of tuberculosis we found no correlation between the sedimentation rate and the Weltmann reaction. Neither could we rely entirely on the sedimentation rate as an index of the prognosis in tuberculosis. The Weltmann reaction, however, is more of a guide in the prognosis of tuberculosis.

In chart 5 (*N.W.*) the patient had a primary tuberculous infection and

improved rapidly. This was reflected in the Weltmann reaction which at first gave a shift to the left, and later made a rapid rise to normal. The coagulation band then shifted to the right which was accompanied by a clinical improvement made by the patient. The sedimentation reaction was rapid throughout the entire course. The patient was discharged from the hospital as an arrested case of pulmonary tuberculosis. In this patient there was an agreement between the clinical course and the Weltmann reaction, and no correlation with the sedimentation rate.

Chart 6 (*J.*) is an example of agreement between the sedimentation rate and the Weltmann reaction, for this patient was admitted to the hospital with a bronchogenic dissemination of a pulmonary lesion which ultimately led to death in about six weeks' time.

In chart 8 (*A.T.*) the patient's condition was not of a serious nature and the Weltmann reaction gave a shift to the right during this time. The patient's temperature was normal and he showed clinical improvement. At this time the sedimentation reaction was rapid, but toward the end of March the patient's temperature began to rise, and he developed a cough. The sedimentation rate approached normal and the Weltmann reaction went more toward the exudative zone. In this example, if one were to depend upon the sedimentation reaction, one would be led to believe the patient was improving clinically. This was not the case; the Weltmann reaction was in the exudative zone and paralleled more the clinical course of the disease.

In chart 9 (*W.W.*) we presented the clinical course of a patient who showed a Weltmann reaction in the exudative zone. The sedimentation reaction although slightly rapid became normal and toward the end of March the sedimentation reaction rose rapidly and the Weltmann reaction again returned to the exudative zone.

Both patients, *A.T.* and *W.W.*, were transferred to the tuberculosis sanatorium, and an examination of their charts indicates the rapid rise and fall of the sedimentation rate from the normal to the abnormal zones. The Weltmann reaction shows a slight rise to the normal zone and correlates the clinical picture more so than does the sedimentation rate.

## MECHANISM OF THE WELTMANN REACTION

As to the mechanism of the Weltmann serum coagulation reaction, very little is known. The same may be said about the chemistry of the changes occurring in the heat coagulation of protein. However, several factors may play a rôle. One must take into consideration the nature

and amount of the protein in various disease conditions, the hydrogen ion concentrations, and the electrolytic content of the surrounding medium. Each protein has its optimum pH and electrolytic threshold. We (15) have shown in a previous publication that the hydrogen ion concentration of the solutions used in the Weltmann reaction plays no rôle in the mechanism of the coagulation band. In chart 15 we have compared the blood pH with the Weltmann reaction and it is apparent that some correlation exists, but no direct relationship. When the test was repeated daily over a period of many months, the patient's blood pH was within normal range, but the fluctuations of the hydrogen ion concentration seemed to have their reflection in the Weltmann coagulation band. This means that, when the two tests are repeated daily over a prolonged period of time and the blood pH drops toward the acid side, the Weltmann reaction usually is elevated or to the right; conversely, when the blood pH goes up toward the alkaline side, the Weltmann reaction goes down or gives a shift to the left. The reason for this phenomenon is difficult to explain. We believe that the blood pH in no way affects the degree of the coagulation band, but both reflect the underlying changes.

Just what rôle is played by the electrolytes of the serum in the mechanism of the Weltmann reaction is difficult to estimate.

Kretz and Kudlac (16) found that the calcium and chloride content of the serum had no effect on the coagulation band.

Several investigators have claimed that the serum proteins have an effect on the coagulation band, and that in such conditions where the globulin fraction is increased, and the albumin fraction is decreased, or when there is an inversed albumin-globulin ratio, the Weltmann reaction goes toward the left. It is believed by these investigators that there must be some correlation between the inversed albumin-globulin ratio and the length of the serum coagulation band. Our results (15) comparing the albumin-globulin ratio and the serum coagulation band do not agree with the observations of Massobrio and de Michelis (17) who have done work along similar lines. We have obtained as many Weltmann reactions with a shift to right or left, when the albumin-globulin ratio was normal or reversed.

The fact remains that with an exudative process such as a nephrotic syndrome, where the coagulation band is to the left in the exudative zone, the albumin-globulin ratio is reversed. In cirrhosis of the liver the coagulation band is to the right, or in the fibrotic zone, and here too

in some cases the albumin-globulin ratio is reversed. Our conclusion, therefore, is that there is no essential relationship between the total serum protein, the albumin, globulin and the albumin-globulin ratio with the Weltmann reaction.

## CONCLUSION

The Weltmann serum coagulation test is of importance in distinguishing between exudative and productive changes. The technique is simple, and the method is described in the text. In general, acute inflammatory and exudative conditions give a shortened coagulation band or a shift to the left. In chronic diseases, characterized by fibrotic changes, in the healing stage of acute infection, and in parenchymal liver damage, the coagulation band tends to be lengthened, or results in a shift to the right. The coagulation band does not always parallel the sedimentation rate. In tuberculosis the Weltmann coagulation test is of importance because it can be used as a guide in the course of and in the prognosis of the disease. It reflects tissue changes that occur in the body. Exudative changes in tuberculosis are manifested by a shortening of the coagulation band, while fibrotic changes are accompanied by a prolonged coagulation band. When exudative and fibrotic changes occur in the lung at the same time, as happens frequently in tuberculosis, the Weltmann reaction may not be of great assistance. The two divergent processes occurring at the same time result in the coagulation band striking the normal zone. In miliary tuberculosis, peritoneal tuberculosis, and in meningeal tuberculosis, the Weltmann reaction gives a shortening of the coagulation band in the exudative zone. Isolated bone tuberculosis is accompanied by a normal or prolonged coagulation band and is reflected in the fibrotic zone. There is a correlation between the blood pH and the Weltmann reaction, but we believe that both of these changes may be directly related to the underlying process. We have applied the Weltmann test not only to tuberculosis in the minimal, moderately advanced and far advanced stages, but also to the complications that occur in pulmonary disease. We have also employed the Weltmann reaction, and compared it with the sedimentation rate, in several examples of various types of tuberculosis over a prolonged period of time. The results are charted in the text. Although we are unable at the present to explain the mechanism of the Weltmann serum coagulation reaction, we believe that this test is of importance in the diagnosis and prognosis of disease, particularly in tuberculosis.

## REFERENCES

(1) WELTMANN, O.: Med. Klin., 1930, *26*, 240.
(2) LEVINSON, S. A., KLEIN, R. I., AND ROSENBLUM, P.: Jour. Lab. & Clin. Med., 1937, *23*, 53.
(3) WINTROBE, W. W., AND LANDSBERG, J. W.: Amer. J. Med. Sc., 1935, *189*, 102.
(4) PETERSEN, W. F.: The patient and the weather, vol. IV, part 2, 1937, Edwards Bros., Ann Arbor, Michigan.
(5) MIKITRA, A., AND TYNDEL, M.: Beitr. Klin. Tuberk., 1934, *84*, 265.
(6) JORES, A., AND STRUTZ, H.: Deutche med. Wchnschr., 1936, *62*, 92.
(7) VOIGTLÄNDER, W.: Klin. Wchnschr., 1934, *13*, 1718; Klin. Wchnschr. 1934, *48*, 1718.
(8) DISSMANN, E.: Beitr. Klin. Tuberk., 1934, *84*, 270.
(9) NIZEGORODCEW, M.: Abstracted in Zeitr. f. Tuberk., 1936, *76*, 62.
(10) ALONSO, J. A.: Abstracted in Zeitr. f. Tuberk, 1936, *76*, 61.
(11) BARSOTELLI, L., AND POGGIONI, D.: Abstracted in Zeitr. f. Tuberk., 1936, *76*, 62.
(12) SCHNEIDERBAUR, A.: Wien. klin. Wchnschr., 1933, *46*, 390.
(13) FRIEDMANN, E.: Klin. Wchnschr., 1935, *4*, 132.
(14) SCHERLEITNER, P.: Wien. med. Wchnschr., 1932, *82*, 1276.
(15) LEVINSON, S. A., AND KLEIN, R. I.: Ann. Clin. Med., (in press).
(16) KRETZ, J., AND KUDLAC, O.: Zeitr. f. klin. Med., 1935, *127*, 590.
(17) MASSOBRIO, E., AND DE MICHELIS, U.: Minerva Med., 1934, *1*, 147.

# INTRACUTANEOUS REACTIONS AGAINST ANTISERUM IN TUBERCULOSIS

H. J. CORPER[1] AND C. B. VIDAL[1]

The recognition of the existence of a specific immunity in tuberculosis has led to numerous efforts to analyze the phenomenon and to translate this information into elemental tests that might be rapid of performance and yield practical information.

The search for significant and consistent antibodies in the blood of tuberculous individuals against the so called toxic substances of the tubercle bacilli has not yielded proof of the production of true toxins or the presence of humoral antibodies against such toxins, at least to the extent of being of practical significance.

About a decade ago, encouraging observations were recorded (1) on the existence of a filtrable labile toxin produced by the tubercle bacillus which gave rise to definite skin reactions in tuberculous patients and guinea pigs. The toxin could be inactivated at a temperature of 70° to 73°C. for one hour. Intraperitoneal injection of small amounts of this toxin filtrate in tuberculous guinea pigs caused typical toxic symptoms. Immune or antitoxic sheep serum was produced by repeated injections of filtrable toxin element of the tubercle bacillus. Such serum neutralized the demonstrable skin reaction caused by the toxin, whereas normal sheep or rabbit serum failed to accomplish this. The intraperitoneal reactions of toxin filtrate in the tuberculous animal were also prevented by immune serum but not by normal serum. From experiments (2) in normal and tuberculous guinea pigs, using an immune goat serum prepared by the intracutaneous injections of toxic filtrates over a period of two years, it was concluded that the reactions obtained with toxic filtrates were unlike those of tuberculin. The immune goat serum contained antibodies that were demonstrable in the skin by passive transfer to the tuberculous animal; immune goat serum neutralized toxic filtrates in varying proportions; and, when such proportions of material permitted, a simultaneous reaction of passively transferred local allergy occurred. In the normal guinea pig, these phenomena were not ob-

[1] Research Department, National Jewish Hospital at Denver, Colorado.

served; filtrates prepared from focal tuberculous tissues were inactive. Toxic filtrates of tubercle cultures appeared to contain antigenic and allergenic substances. Filtrates prepared from emulsions of local tubercles in the skin of infected guinea pigs did not cause local and general reactions.

In 1932, there appeared, as an accurate and earlier diagnosis for tularaemia, a new intracutaneous reaction (3) in which chemically detoxicated bacilli were used. The intracutaneous test was found to be the earliest diagnostic aid for tularaemia, occurring earlier than the agglutinins.

In continuation of the foregoing, a new intracutaneous antiserum test was presented (4) in 1935 which was considered a specific response to bacterial material independent of serum sensitization. A close study revealed two entirely different reactions to the intracutaneous injection of specific antiserums in certain infections. One was the well understood serum protein reaction (of allergy or anaphylaxis); and the other, an erythematous-oedematous reaction, characterized by simple erythema with central oedema and complete absence of urticaria, is a specific response to bacterial products wholly unrelated to serum sensitization. The latter reaction usually appears promptly, within 2 to 4 minutes, is maximal in 20 to 25 minutes, and often is intensified after about 6 hours. No constitutional symptoms accompany the local reactions. The reaction is seen only when a patient with a given bacterial infection is tested with an antiserum specific for that infection. Usually all skin tests are made with serums diluted 1:10. It is specific in tularaemia, brucellosis, lymphogranuloma inguinale, streptococcus infections, gonococcus infections, staphylococcus infections, typhoid fever and tuberculosis. How extensive the experience had been in tuberculosis was not noted in this paper nor have animal experiments been found in the literature bearing on this reaction. Its relation to the tuberculin reaction was also undisclosed, except that it may be inferred that the tuberculin reaction probably resembles specific protein reactions, and it may have been considered as such.

The experiments to be recorded here for their value in elucidating the specific and immune reactions occurring in tuberculosis were inspired by the foregoing observations. These experiments were performed on guinea pigs, rabbits, dogs and human beings.

In pursuing such experiments, it may be well to recognize certain obvious facts, the pitfalls of which must be avoided in any interpretation of results of certain tests. Outstanding among these is the allergic or

anaphylactic hypersensitive reaction. The essential features of this reaction are now fairly well understood; and it is not our purpose to try to interpret the similarities or differences between anaphylaxis and allergy but rather to accept the broader interpretation of their being identical as has been done by Vaughan (5) in 1936. Vaughan points out that there is no fundamental difference between clinical allergy and experimental anaphylaxis, that the allergic response is not limited to protein but may be elicited by a large variety of nonprotein substances, and that the response of the allergic person differs from the nonallergic in degree and not in kind. "Allergy is not a pathologic state. It is a pathologic exaggeration of a normal physiologic response."

The reaction to a foreign organic material can occur in response to the body fluids and tissues of closely related species of animals, and yet rarely does it occur in response to tissues or fluids transferred from the same animal or animal species. In extensive preliminary animal experiments, we endeavored to elucidate general anaphylactic reactions by injecting guinea-pig tissues and blood intravenously into guinea pigs and then giving a second intravenous injection (also by other routes) of ground tissues or filtrates from these tissues or the clear fluid from such tissues one to two months later. In no case were we able to elicit a response resembling anaphylaxis or allergy. However, the use of tissues, blood or serum from another animal species, upon second injection, after two weeks to two months, readily elicited the reactions well known as characteristic of anaphylaxis. The same results were obtained in the rabbit and the dog.

Another reaction pertinent to specific antiserum reactions is that occurring quite strikingly, especially in the human being, even on the first injection of certain foreign sera. This will be mentioned more fully in the control results in the following tests on human beings tested with normal goat serum. With the recognition of the possible sources of error in performing specific intracutaneous antiserum reactions, it was decided at first to perform all tests with sera from the same animal species in order to eliminate as far as possible the source of error due to the use of sera from other species.

*Experiments on guinea pigs:* In order to obtain serums appropriate for testing the presence of intracutaneous antiserum reactions, a series of guinea pigs designated as donors was given injections of avirulent and virulent human tubercle bacilli in appropriate amounts and by various routes. The avirulent human tubercle bacilli were injected in amounts

(about 1 to 10 mgm.) exceeding that necessary to produce a definite specific immunity against an appropriate virulent infection (about 0.000,01 mgm.). The virulent human tubercle bacilli were used in amounts (0.000,001 to 0.001 mgm.) producing a generalized disease in about two to four months and consistent with the development of antibodies, yet incapable of producing an overwhelming generalized disease. Thus, the serum obtained from these animals probably would not contain excessive amounts of tuberculin-like substances, and the normal reactivity of the animal probably would not be lowered to a nonreacting level of terminal or acutely lethal disease. Serum was obtained from the donors at different intervals up to six months after injection, and 0.1 cc. of these sera was injected intracutaneously into the recipient guinea pigs in full strength and in dilution of 1:10 (1:100 in preliminary experiments) using every precaution to give uniform injections and to make possible adequate comparison with the normal serum controls which were injected intracutaneously in the same manner.

The avirulent human tubercle bacilli used in these experiments were incapable of producing macroscopical tuberculosis when given intravenously to guinea pigs in fine suspension in amounts of 1 to 10 mgm. while the virulent bacilli produced a generalized disease in guinea pigs within three months when given intravenously in fine suspension in as small a dose as 0.000,000,01 mgm. (6). The recipient guinea pigs used for intracutaneous testing consisted of four groups of animals: normal control guinea pigs, guinea pigs which had received an intravenous injection of 1 or 10 mgm. of avirulent human tubercle bacilli, guinea pigs which had received an intravenous injection of about 0.01 mgm. of avirulent human tubercle bacilli, guinea pigs which had been infected subcutaneously with 0.001 mgm. of virulent human tubercle bacilli (strain 127), and guinea pigs infected subcutaneously with 0.000,001 mgm. of virulent human tubercle bacilli (strain 127). Although some of the guinea pigs receiving the larger amount (0.001 mgm.) of the virulent human tubercle bacilli succumbed to the infection before the termination of the tests, those given the smaller amounts (0.000,001 mgm.) survived for the final tests at the six-months interval.

It is unnecessary to present the detailed experimental results since no evidence was obtained of the existence of an intracutaneous specific reaction against tuberculosis antiserum in the guinea pig. Reactions were never noted although the animals were carefully observed for the first six to eight hours after intracutaneous injection and regardless

of whether avirulent or virulent human tubercle bacilli had been injected into the donors or recipients.

Repeated injections of avirulent human tubercle bacilli subcutaneously or intravenously, consistent with maintaining the guinea pigs in good physical condition, also failed to produce substances in the serum which would elicit any type of intracutaneous reactions in the recipients injected with avirulent or virulent human tubercle bacilli.

*Experiments on rabbits and dogs:* The experiments performed on rabbits and dogs were similar to those outlined above with the exception that these animals tolerated much larger injections of both avirulent and virulent human tubercle bacilli. The dogs particularly could be given repeated injections extending over longer periods of time, in some cases exceeding one year.

In spite of the prolongation of these experiments as compared with those in the guinea pigs, no evidence was obtained in these animals for the existence of specific antiserum reactions in tuberculosis following intracutaneous testing with the sera obtained from dogs or rabbits which had been given either single or repeated injections of fine suspensions of virulent or avirulent human tubercle bacilli. In dogs, profound lethal infections from large amounts of virulent human tubercle bacilli also failed to disclose any specific reactions in the tests whether these dogs were used as recipients or donors.

We did not use chemically detoxicated tubercle bacilli in our experiments because we felt that it would prove fruitless to pursue this phase further since evidence was lacking to encourage elaboration upon the various experiments performed with avirulent and virulent human tubercle bacilli, and especially after trying various animal species. However, since the reactions obtained by others were obtained mainly in human beings and with antisera from animals such as the goat, we thought that possibly certain animal species might react differently from human beings. The attempts to prepare sera giving specific antiserum reactions in tuberculosis made it seem advisable to obtain a suitable antiserum which had given reactions in the hands of other investigators. The serum supplied was prepared in a goat that had received repeated injections of so called detoxicated tubercle bacilli, the injections extending over several years. For control comparison, we used serum from a normal goat.

*Tests with a specific tuberculosis antiserum in human beings:* The normal goat serum and antiserum were injected full strength and in a 1:10

dilution in the forearm of the subject. The human subjects were all adults and included normal and tuberculous individuals. They were previously tested for tuberculin hypersensitiveness, using the standard P.P.D. of Long and Seibert and prepared by Parke, Davis & Company. Among the five human subjects chosen for the tests, two were normal nontuberculous individuals, negative to the large test dose of P.P.D.; a third was positive to the large dose but not to the small dose of P.P.D.—he had an arrested moderately advanced pulmonary tuberculosis without bacilliferous sputum; while the last two subjects gave a positive reaction to the first dose of P.P.D. and had advanced active pulmonary tuberculosis of many years standing, one of these cases being treated with artificial pneumothorax. Such transient intracutaneous reactions as occurred during the first twenty-four hours in all these five human subjects, with both the normal and the tuberculosis antiserum from the goat, could be considered traumatic. There was no appreciable difference between the reaction to the full strength serum and the 1:10 dilution. The reaction to the fresh normal goat serum, however, was slightly more pronounced than that to the antiserum. This was attributed in part to the possible differences in the ages of the sera and their modes of preparation. No difference was noted in the reactions of the tuberculous subjects and those of the tuberculin-negative normal subjects. However, within a variable period of three days to two weeks, and varying in intensity for the individual subjects, a nonspecific reaction to goat serum was noted. The skin at the site of the intracutaneous injections became extremely sensitive to slight irritation and in some cases itched intensely (pruritus), more so in the area where full strength serum was injected. At a later period, surface desquamation occurred in some cases, and that reaction persisted for several days to a week with final complete subsidence. There was noted, however, in this reaction no specificity in regard to tuberculosis, since the reaction to goat serum occurred alike in normal tuberculin-negative subjects and in tuberculous tuberculin-positive advanced cases of pulmonary tuberculosis.

## CONCLUSIONS

Although it is conceded on the basis of prior experiments (7) that there exists a specific immunity to tuberculosis demonstrable both in man and animals (7, 8), it was found impossible to demonstrate the existence of such immunity by means of any intracutaneous reactions against specific antisera. All attempts proved futile to produce antisera

that would react specifically on intracutaneous injection into animals of the same species (in order to exclude foreign serum reactions). Antisera were prepared in guinea pigs, rabbits and dogs and were injected into animals infected with virulent and avirulent human tubercle bacilli. In human subjects, both normal and tuberculous, with negative and positive tuberculin reactions to tuberculin (P.P.D.), no specific reactions were obtained to antisera. Sera from normal and from immunized goats produced intracutaneous reactions in normal and tuberculous human subjects. These reactions developed after three days to two weeks and persisted several days to a week, varying in intensity.

We are grateful to Mr. Ray E. Stoner for assisting with the technical details of this study.

## REFERENCES

(1) EBERSON, F.: Filtrable toxins of tubercle bacilli and production of antitoxic serum in sheep, Jour. Amer. Med. Assn., 1928, *90*, 260.

(2) EBERSON, F., AND SWEENEY, M. A.: Tuberculotoxins and their significance in allergy and neutralization phenomena, Jour. Immun., 1931, *20*, 395.

(3) FOSHAY, L.: Tularemia: Accurate and earlier diagnosis by means of the intradermal reaction, Jour. Infect. Dis., 1932, *51*, 286.

(4) FOSHAY, L.: Intradermal antiserum tests: A bacterial-specific response not dependent upon serum sensitization but often confused with it, Jour. Allergy, 1935, *6*, 360.

(5) VAUGHAN, W. T.: A theory concerning the mechanism and the significance of the allergic response, Reprint from Medical Papers Dedicated to Dr. Henry A. Christian, February, 1936, p. 711–736.

(6) CORPER, H. J.: The virulence of the tubercle bacilli isolated from the sputum, Jour. Infect. Dis., 1918, *23*, 493.

(7) CORPER, H. J., COHN, M. L., AND DAMEROW, A. P.: Studies on the behavior of the tubercle bacilli within the body, Amer. Rev. Tuberc., 1936, *33*, 679, 694, 701, 709 and 721.

(8) CORPER, H. J., DAMEROW, A. P., COHN, M. L., AND VIDAL, C. B.: Vaccination against tuberculosis—a comparative study in man and animals, Jour. Infect. Dis., 1936, *58*, 158.

# EXPERIMENTAL OLEOTHORAX[1]

D. H. SALEY, H. S. WILLIS AND LUCIA ELLWART

A good many years have passed since the idea and technique of oleothorax were introduced by Mackenzie (1) and refined by Bernou (2). During this period a great deal of experience has accumulated with respect to the use in tuberculosis of the lung and pleura, and the claims for its use have, in the main, crystallized about as follows: (*1*) that a mass of oil in the pleural space maintains the space when obliterative pleurisy impends; (*2*) that oil produces inflammation and thickening of the pleura and thus leads to closure of bronchopleural fistulae and to stiffening of a mobile mediastinum; and (*3*) that gomenolized oil is bacteriocidal or bacteriostatic and thus is a valuable agent in the treatment of empyema.

On the other hand a considerable number of observers have used oleothorax for varying lengths of time only to give it up finally as being of little avail. Recently, Joannides (3) has given a useful and extensive bibliography on the subject.[2]

In 1931 when these several diverse claims were still being promulgated somewhat vigorously, we undertook an experimental study of the question with the thought that further detailed knowledge of the basic pathological response of tissues to oils might be a helpful guide in recommending clinical use of oleothorax. At that time Archibald (4), Young (5), Chandler and Gloyne (6), Waitz (7), Diehl (8) and several others had made significant experimental observations on this question, particularly as to the early tissue reactions. Archibald (4) and Young (5) found very mild reaction to the injection of oil. Chandler and Gloyne (6) injected several kinds of oil into the pleural space of rabbits and produced soft adhesions, granulation tissue, marked cellular response; in

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Joannides (3) has discovered a little-known reference to the use of oleothorax in empyema which antedates Bernou's work by several years. This is the work of Mackenzie (1) who, in 1914, used a light hydrocarbon to replace empyematous fluid without recourse to pneumothorax. Mackenzie suggested that the method might be used in tuberculosis to maintain collapse instead of nitrogen in pneumothorax, then just coming into accepted and fairly wide use.

short, reactions associated with any sterile irritant. They reported rather rapid absorption of vegetable oils and slower but definite absorption of mineral oil. Waitz (7) used vegetable oils, with and without gomenol, in guinea pigs and puppies in which he continued artificial pneumothorax and produced serous effusion, pleural thickening, "villous" pleurisy with granulation tissue and new formed capillaries, subpleural and peribronchial cellular infiltration.

*Materials and methods:* In our experiments we sought to determine the type and duration of reaction of normal rabbits to intrapleural injection of mineral (paraffin) and of vegetable (cotton-seed) oil, each with and without the addition of gomenol and with the oil applied in single and in repeated doses, and in small and large quantity. Altogether 110 rabbits were used. The volume of oil injected ranged from 1 cc. to 25 cc. and the injections numbered from one to five, the latter at weekly intervals. Animals were examined at intervals from 24 hours to 22 months after injection.

In order to be certain that the injection was made into the pleural space, we induced artificial pneumothorax which yielded satisfactory manometric readings. Then we attached a syringe containing oil to the intact needle, made the injection and withdrew the air so that the final response would represent reaction to oil only and not to both oil and air. We repeated this procedure at each injection. After the third or fourth injection it became difficult to obtain an air space. In such event, injections were discontinued. We added a nonirritating dye (Tieman's soluble blue) to the oil in some instances to facilitate a study of absorption, and controlled the possible introduction of infection by use of culture methods, as Archibald (4) had controlled his experiment. Finally, efforts were made to prevent adhesion formation by placing "Amfetin" in the pleural space along with the oil.

*Results:* The constant and almost unfailing result of the placing of oil in the pleural space is inflammation and its sequellae: adhesive pleurisy, adhesions, scar and fibrosis. This occurred almost without exception in these experiments and irrespective of the type of oil used, the quantity and the addition of gomenol. Gomenol was added in strengths of one and five per cent to each of these oils. Reaction was the same to the oils with and those without this addition.

It should be mentioned in this connection that the response to cotton-seed oil differs in two respects from that to paraffin oil: (*1*) it emulsifies, and (*2*) it is absorbed more rapidly. In all other respects each brings

forth the same basic reaction. The description given here of the reaction up to two or three months after injection applies equally to the use of either paraffin or cotton-seed oil; that of later reaction applies to the relatively nonabsorbable mineral oil.

*Gross appearance:* Reactions are plain and obvious upon gross examination. Twenty-four and 48 hours after injection the lung is somewhat retracted and has a bluish cast. It is covered by a grayish-white, mucoid, oily coating obviously composed of oil droplets and fibrin. The entire pleural surface has lost its normal, glistening appearance and is roughened and granular due to fibrinous deposit. Fluids recoverable equal roughly the volume of oil injected. The contralateral side is intact and normal in appearance.

After one and two weeks the abdominal surface of the diaphragm is dark and congested on the treated side, and this half of the organ is retracted toward the thorax. The left thoracic space contains a few cubic centimetres of oily fluid and small, oily masses or plaques of fibrin which float in the fluid. The pleura of the lung, chest-wall, mediastinum and diaphragm is flecked with small white gobs that resemble fat, numbers of them being attached to each other by strands of fibrin. Some of these are as large as 5 mm. in diameter. Occasionally a bulky mass of oily fibrin attaches to one of the pleural surfaces. The retracted lung is attached at numerous sites to the pericardium, chest-wall and diaphragm by soft, flimsy, oleogenous adhesions. Where cotton-seed oil has been injected, the remaining oil has become emulsified and is milky in appearance. The paraffin oil remains clear and transparent.

When oil has been in the pleural space for three and four weeks, the reaction is much like that just described but, in addition, plastic pleurisy or pleural thickening becomes more marked and universal, adhesions tend to be more extensive and less friable and the volume of oil is somewhat reduced. Adhesions anchor visceral to parietal surfaces; they pull the diaphragm toward the costal wall and thus obliterate the costophrenic angle; they pull the pleural fold which separates the epicardial lobe from the other lobes and forms the caudal portion of the mediastinum, so as to enlarge that space sufficiently to hold several cubic centimetres of oil. At times a few drops of oil penetrate the mediastinum to reach the contralateral space and arouse there a pleural reaction.

As time passes, further slight changes are to be observed. Acute inflammatory reaction yields to dense fibrous tissue. After oil has been in the chest for 3, 4, 5 or 6 months, adhesions are thick and firm. Of

irregular shape, they lie in many areas and planes and wrap the lung in such a way as to form pockets which contain small amounts of sacculated oil. They cause contraction of the lung, distortion of the thoracic tissues, retraction of the diaphragm and diminution of the thoracic space on the affected side.

This condition represents the average. However, it is interesting to observe an occasional thorax which contains clear oil and only a few small, string-like adhesions.

The animals which have lived a long time after injection (15 to 22 months) present usually the picture of extensive thoracic distortion from adhesions, with small sacs of clear oil here and there. However, the proportion of animals with little or no oil and scant reaction is greater in this latter group. The last animal killed in this series had lived 22 months after injection of 5 cc. of paraffin oil and presented only a half dozen hair-like, strong adhesions and moderate thickening of the mediastinal folds. There was no oil. The lungs were of normal color and the pleural surfaces everywhere were normally glistening. The costophrenic angle was normal.[3]

The gross appearance of the effects of oil is illustrated in figures 1 and 2. Figure 1 illustrates a bulky mass of fibrin against the mediastinum and a thick fibrinous deposit on the parietal pleura of the left side. This animal was killed one week after injection of 2 cc. of paraffin oil containing one per cent gomenol. Figure 2 shows extensive fibrosis and adhesion formation 16 months after injection of 4 cc. of 5 per cent gomenol in paraffin oil. In several animals which had lived from 12 to 22 months after injection of oil, the reaction was much less marked than that shown in this figure.

*Microscopical appearance:* The microscopical appearance may be anticipated from the gross picture. At 24 hours an early outpouring of fibrin leads to thickening of the pleura over wide areas, the thickened, undifferentiated matrix containing many vacuoles (oil), many polymorphonuclear leucocytes, many large mononuclear phagocytes and small round cells. Frequently at 24 hours and usually at 48 hours after injection, an abundant lattice work of fibrin has been deposited on the pleura. This meshlike structure encloses spaces of a great variety of size and shape, apparently occupied, before fixation, by oil droplets.

[3] Observations such as this have caused us to speculate upon the resorption of adhesions or other scar tissue, once the irritant is removed. The disappearance of supposedly pulmonary scar tissue is not uncommonly seen in serial X-ray films of the tuberculous lung. Studies on this question are in progress.

FIG. 1

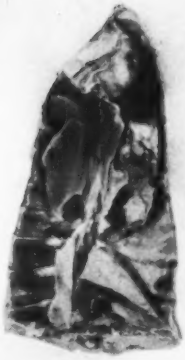


FIG. 2

FIG. 3

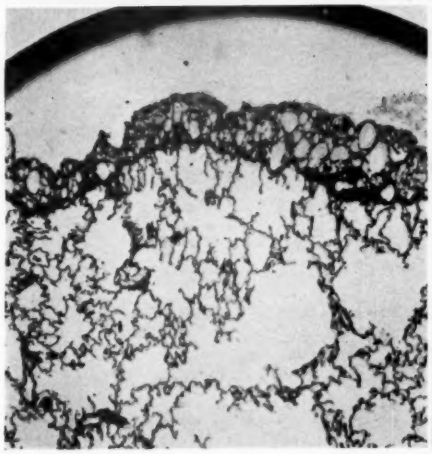


FIG. 4

PLATE 1

FIG. 1. Rabbit injected with 2 cc. of 1 per cent gomenol in paraffin oil and killed one week later. Masses of fibrin adhere to the pleura and bind the heart to the sternum. A fibrin coating is applied to the costal pleura.

FIG. 2. Rabbit injected with 4 cc. of 5 per cent gomenol in paraffin oil and killed 16 months later. Right side is normal. Left (injected) side shows diaphragm retracted toward the thorax. Lung is bound to the chest-wall at many points.

FIG. 3. Low-power microscopical view of pleural reaction 3 weeks after injection of 2 cc. of paraffin oil into the pleural space. General description is given in the text.

FIG. 4. Low-power microscopical view of pleural reaction 7 months after injection of 16 cc. of 1 per cent gomenol in paraffin oil. See text for description.

After ten days or two weeks the thick fibrinous plaques on the surface of the pleura have become organized. Newly formed capillaries are numerous, as are fibroblasts and there is beginning formation of collagen fibrils. Superimposed upon these organized plaques are masses of undifferentiated fibrin and the more or less necrotic (?) cells of the original exudate. Vacuoles representing oil droplets are numerous in this undifferentiated and organized tissue.

As time passes the reaction becomes less cellular, more thread-like and fibrous, remaining meantime extensively vacuolated. After oil has been in the pleura for months, both visceral and parietal pleurae become moderately but densely thickened. Figures 3 and 4 illustrate the early and later stages of the pleural reaction. In figure 3 the typical pleural reaction at 3 weeks after injection is shown while the more fibrotic, less cellular reaction at 7 months may be seen in figure 4.

The lung gives evidence of elastic retraction, alveolar walls are thickened, some of the alveoli are moderately flattened or otherwise of distorted shape and contain small round cells. These cells crowd the pleural lymphatics and are distributed in moderate numbers through the deeper pulmonary tissue, along with numerous macrophages. Oil droplets have been seen in the blood vessels of the lung by several observers (9) but none were observed in these experiments. Pulmonary tissue approaches the normal after all oil has been absorbed.

The question may be raised whether these reactions arose solely as a response to oil or to oil and infection that could have been introduced into the pleural space by faulty technique. We believe that bacteria had nothing whatever to do with the observed reactions. Smears and cultures were made at every autopsy and in only one animal in more than 100 were bacteria demonstrated. In this one instance there was extreme congestion of all pleural surfaces in addition to the usual reaction to the oil which the other animals showed.

*Absorption of oil:* During the course of the experiments it became clear that cotton-seed oil disappears from the chest a few weeks after it is introduced. At the first week after injection serous effusion is present, and effusion and oil may measure as much or even a little more than the volume of oil introduced. But by six or eight weeks after injection of 5 cc. of oil only a few drops remain and by 12 weeks it has nearly always disappeared completely. It became equally clear that paraffin oil remains in the chest for a very long time but tends eventually to be absorbed. In an occasional animal only a few drops remain at 12 or

16 weeks, although the rule is to find well over one-half the amount injected six months after injection. When 15 or 20 cc. of paraffin oil are injected, more than one-half and often more than three-fourths the volume is recoverable 12 months after injection. In only one instance had all the oil disappeared when the animal was killed at six and one-half months. In one instance, where the same volume was used, only a few drops were recoverable in 16 months. Most of the other cases revealed 10 cc. or more when the animals were sacrificed. In one animal in which 5 cc. had been injected, none was found 22 months later. It has been intimated above that adhesions seem to disappear after the oil has been absorbed.

To the mechanism of absorption, only secondary attention was given and this for two reasons: (*1*) frozen sections of fresh oil-containing tissues could not be prepared, and the oil was lost in the routine histological technique; (*2*) in many instances the thoracic cage was saved with the lungs intact so that the regional lymph nodes were not examined in all cases. However, 25 per cent of the retromanubrial and a somewhat larger percentage of the tracheobronchial lymph nodes examined contained oil or pigment in amount sufficient for gross detection. This indicates lymphatic absorption from both the parietal and visceral pleura. No oil or pigment could be seen in sections of the kidneys, liver or spleen of the oil-treated animals. None was detected in the lung itself although an occasional small vacuole in a lymphatic and small blood vessel suggested absorption and transportation of oil by these two systems.

Several authors have stated that oil may be absorbed directly. Diehl (8) thought absorption occurred directly into swollen endothelial cells without the intervention of leucocytes. Hayes (10) questioned the wisdom of using vegetable oil because of its irritating effect upon the pulmonary tissues after it is absorbed into the lung. Waitz (7) reported inflammatory reaction deep in the lung as a result of absorbed oil. Binet and Verne (11) believed that phagocytes carry the oil droplets through lymphatics, and Bettini (9) that droplets are carried in the blood. Several writers, among them Bratiano and Bratiano (12) and Chandler and Gloyne (6), have concluded that oil is subject to lipolytic action.

It has been claimed that the introduction of amniotic fluid into the abdomen prevents the formation of adhesions after operations (Warren (13)). We wondered whether this substance might prevent the development of the extensive adhesions which so constantly follow injection of

oil into the pleural cavity. To that end we injected "Amfetin"[4] with oil and at weekly intervals thereafter for as long as 12 weeks. In some of the 15 animals thus treated somewhat fewer adhesions were present than in the control animals, but we could not demonstrate that this agent prevented the formation of adhesions under the conditions of the experiment. Amfetin did appear to hasten the absorption of oil although longer experiments might have been more conclusive.

## SUMMARY AND CONCLUSIONS

Oleothorax has been advocated as a clinical procedure on three counts, namely: (*1*) that it will maintain collapse of a lung under pneumothorax in which obliterative pleurisy impends; (*2*) that it irritates pleural surfaces and thus leads to pleural thickening, closure of bronchopleural fistulae and to stiffening of a herniating mediastinum; and (*3*) that gomenolized oil is antiseptic and aids in healing of tuberculous and nontuberculous empyemata.

Experimental work abounds which proves some of these contentions. It was to learn more of the essential pathological reaction elicited by oil in the pleural space that the work now reported was undertaken. From the results of this work it is clear that oil may produce extreme grades of fibrinous and fibrous pleurisy with marked visceral distortion and displacement. It is clear, also, that vegetable oil is absorbed within a few months of its introduction, and that mineral oil remains much longer in the chest and usually is present in some volume a year or a year and a half after injection. The latter appears to be absorbed eventually, however. The mechanism of absorption is not entirely understood although the pleural endothelium and the phagocytic cells may absorb oil and the lymphatics and blood vessels may absorb and transport it. It seems probable that adhesions are absorbed after the irritating oil has been absorbed.

No conclusions are made from this work insofar as it concerns therapeutic application of oil in man except to point out the fact that oil in itself establishes a pathological condition of the animal tissues which is far from normal and, at times, far from desirable. No implication can be made from this work as to the desirability of oleothorax in human cases of empyema.

[4] This product, which is bovine amniotic fluid, was generously furnished us in abundant amount by Eli Lily & Co.

## REFERENCES

(1) MACKENZIE, K. A. J.: A preliminary report on a method of treating empyema without resort to pneumothorax, Trans. Amer. Surg. Assn., 1914, *32*, 655.
(2) BERNOU, A.: L'oléothorax thérapeutique, Bull. Acad. Méd., (3rd series), 1922, *87*, 457. See also: Rev. Tuberc., 1926, *7*, 345.
(3) JOANNIDES, M.: Oleothorax in collapse therapy of pulmonary tuberculosis, Amer. Rev. Tuberc., 1936, *34*, 561.
(4) ARCHIBALD, E.: A note on compression of the lung by paraffin oil in the pleural cavity, Ibid., 1922–23, *6*, 898.
(5) YOUNG, J. S.: Experimental production of metaplasia and hyperplasia in serosal endothelium, etc., Jour. Path. & Bact., 1928, *31*, 265.
(6) CHANDLER, F. G., AND GLOYNE, S. R.: Oleothorax, Tubercle, 1926–27, *8*, 563.
(7) WAITZ, C.: Experimentelles zum Oleothorax, Beitr. Klin. Tuberk., 1930, *73*, 59.
(8) DIEHL, K.: Die physikalischen und physiologischen Grundlagen des Oleothorax und ihre Folgerungen für die Klinik, Ztschr. f. Tuberk., 1929, *53*, 514.
(9) BETTINI, D.: Ricerche sperimentali sull' oleotorace, Riv. di pat. e clin. d. tuberc., 1933, *7*, 400. Quoted from Hayes (10).
(10) HAYES, J. N.: Oleothorax, clinical and experimental, Ann. Int. Med., 1935, *9*, 779.
(11) BINET, L., AND VERNE, J.: Les processes histologiques de l'absorption des graisses par la plèvre, Bull. d'histol. appliq. à la physiol., 1925, *2*, 14.
(12) BRATIANO, S., AND BRATIANO, C.: L'absorption des graisses animales par la plèvre, Ibid., 1928, *5*, 133. Quoted from Hayes (10).
(13) WARREN, S.: Effects of amniotic fluid on serous surfaces, Arch. Path., 1928, *6*, 860.

## EDITORIAL

### Has Tuberculosis Treatment Been Effective?

The valuable study by Drolet (1) on the trend of case fatality rates in tuberculosis again plumps the question about the factors to be credited for the striking retreat of this disease, particularly in recent time. Since these are patently numerous and since they operate at various times and at various places with a varying interrelationship, a precise evaluation can never be had, and opinions, therefore, will differ. That the more abundant life has been a powerful force none can deny, though debate could be held about the degree of this power and the definition of abundance. The important thing is to recognize all the useful measures which may be turned with some effectiveness against tuberculosis, to become familiar with their limitations, and to decide how best they may be applied under varying conditions. Whether we deal with communities or with persons, the control of a disease like this is a matter for individualization, that is, identifying the forces of resistance which naturally tend to hold off the invader and then applying with skill and discrimination the measures which are known to augment or accelerate these forces. Drolet's analysis logically raises the question whether, beyond isolating the infectious case, sanatorium or surgical treatment has been a significant factor.

A statistical study cannot take into into consideration such imponderables as the educational value and the scientific contributions of the sanatorium, yet these are among its best assets. The effectiveness of treatment to improve the quality and productiveness of the patient's living during his remaining years cannot be figured, nor can there be an accurate estimate of the preventive value of sending the patient back home trained to avoid spreading the infection among his family, or no longer infectious. In fact, such a statistical examination is not intended to and cannot disclose the effect of treatment in specific cases or classes of cases. Nevertheless, it should and does throw some light on the total effect in large communities, and this should be welcomed since every physician hopes that his effort to heal will have broad and remote as well as specific and immediate significance. Some may question the re-

liability of a ratio between new cases reported and deaths as a basis of analysis, especially since reporting is known to be incomplete. Whatever the error may be, however, it is rather minimized by the scope of the figures and the long time covered. The study, therefore, merits cogitation, taken at its face value.

For examination, one of Drolet's conclusions might be restated more specifically; namely, it is not demonstrated that the treatment of advanced tuberculosis, as practiced during this time, has had a very significant effect on case fatality rates. The reason for this is the difference between the results of treatment of the early and the advanced case and the difference between good and bad treatment. It must be considered first that the sanatoria of our country regularly receive eighty per cent or more of their cases in an advanced stage, a fact reaffirmed by the comprehensive survey reported by the American Medical Association in 1935 (2). It is the general experience that most deaths in institutions occur within a few months after admission. In most of the fatal cases, therefore, it can hardly be said that the treatment applied is calculated to be curative, but as long as this situation prevails the sanatorium fatality rate is not likely to improve much. Further, it has long been known that all but a few of the patients with advanced tuberculosis eventually die of that disease regardless of the manner of treatment. Treatment, therefore, is designed to cure, if possible, but mainly to prolong life and make it bearable and, to a degree, productive. Sanatorium care for the advanced case has been costly and generally inadequate, the average length of stay being, on the average, considerably less than six months. Because of their high cost, infirmary space and nursing personnel are not sufficient to permit the prolonged rest in bed which is desirable. Surgical therapy has been added, but, if Drolet's figures have a meaning, they fail in the large to show an appreciable result. This suggests a weakness in the practice, because other more narrow but more intensive studies have proved the value of modern treatment even in advanced cases. The faults seem not to be so much in the treatment as in the manner of its application, and it is well to attempt to identify some of these. Because of pressure from lack of hospital accommodations, anxiety of the patient and his family, and sometimes because of a misconception of the healing of tuberculosis, the rest cure many times has been prematurely terminated under the delusion that collapse of the lung is a complete substitute. In other instances, time has been wasted in waiting for the rarely realized benefits of relatively feeble measures (such

as phrenic nerve interruption in advanced cavernous tuberculosis), yet this would be recorded as a failure of collapse therapy. Sometimes, something is done solely in the belief that something is better than nothing, but this, as a rule, salves the physician's tender and unregulated conscience more than it does the patient's sores. Wiser heads appreciate that, in cases that cannot be rehabilitated, it is better to abstain from surgery of any kind lest the patient's disability be increased and his life shortened. Development of new methods of surgical and other treatment should and will go on, but it is equally important to train the individual physician to select the combinations which best serve the interest of the individual patient. Teaching must emphasize that, unless rest treatment can be applied properly and for adequate time to support old or new adjuvant measures, the ultimate results are not likely to be impressive.

The early or "minimal" case in which sanatorium treatment is immediately and in the long run most effective, but for which it is not usually employed, is a problem with many differences. Proper treatment of the early lesion is usually an effective safeguard against the development of advanced disease, and, therefore, has always proved to be the highest achievement of the healing art in this field. It is strange then how human psychological reactions so often sprout some excuse why such treatment should not be given. The patient, perhaps, cannot bear to face the possibility of tuberculosis and stays away from his doctor until alarming symptoms force action—too late. The physician, diagnosing the early infiltration in a young person, sometimes shrinks from advising a rest cure with its economic consequences and waits to be convinced by the appearance of unmistakable symptoms and a positive sputum—the heralds of advanced disease. The sanatorium, too often, has its infirmary filled with late cases and keeps the young patient with a soft patch of bronchopneumonic tuberculosis ambulant, knowing that, if a cavity develops, it can probably be closed with pneumothorax. The conception grows, more in the minds of economists than of physicians, that the rest cure can be eliminated and that collapse therapy and a couple of weeks of repose will solve the problem, allowing the patient to go on with his work, presuming, without proof, that money will be saved for him and the community. All this, in spite of the knowledge, proved more than anything else in the tests of therapy that complete treatment of the early case—not the rest cure alone, but combined with

collapse of the lung when indications exist—for an unhurried time promises, more than any substitute short cut, a lasting cure for the patient and ultimate control in the community. Otherwise, it is questionable how much case fatality rates may change, and, beyond isolating the infectious case, whether treatment in the future can be credited in the broad sense with increasing effectiveness.

REFERENCES

(1) DROLET, G. J.: Present trend of case fatality rates in tuberculosis, Amer. Rev. Tuberc., 1938, *37*, 125.

(2) The tuberculosis survey, Jour. Amer. Med. Assn., 1935, *105*, 1855 *et seq.*

J. B. A., JR.

# STATISTICAL BASIS OF ERRORS IN IMMUNITY TESTS

WILLIAM N. BERG

*Purpose:* To point out (*1*) sources of error in the longevity test for immunity in guinea pigs, and (*2*) conditions for their removal.

The following immunity test is typical of several published from the X Tuberculosis Research Laboratory and from other similar institutions. Ten guinea pigs were "immunized" with an antituberculosis vaccine. These 10, together with a similar control group of 10, were then infected with equal doses of virulent human tubercle bacilli. The immunized animals lived 469, 369, 292, 266, 246, 230, 185, 175, 152 and 97 days after infection. Their mean (or average) days of life following infection were 248 days. The controls lived 409, 259, 161, 149, 139, 123, 113, 102, 54 and 49 days after infection. Their mean days of life were 156 days. The difference between the two means, 248 less 156, or 92 days in favor of the immunized group, was interpreted as due to the protective potency of the vaccine, on the commonly erroneous assumption that both groups originally had the same mean expectation of life.

What would the above difference of 92 days, have been if the experiment were blank, that is, if only sterile salt solution had been used for immunization and only sterile sugar solution for infection? Since this difference may be, and frequently is, due to random sampling of guinea pigs, a simple statistical method was described in a previous publication (1) for testing the significance of a difference between means. Such testing is necessary in many researches where a conclusion is based upon a difference between means (or averages) of samples drawn from a large population.

When should immunity tests be planned and analyzed by statistical methods? Those early investigators who sought a biological or chemotherapeutical product that would effect a complete prevention or cure of tuberculosis had little need for statistical methods. When the search began for acceptable products, which, while they fell short of the above objectives, would still have some demonstrable potency, it was not realized that an apparently slight change in objectives called for a profound change in the method of the experiment. Immunity tests on lab-

oratory animals made 50 years apart were the same, in spite of changed objectives.

*The error:* A fundamental in the statistical study of sampling is that two or more samples drawn at random from a given large group will have different means. When a dealer is asked to forward 40 guinea pigs of similar weight or age to a laboratory, and these are divided into a group of 20 controls and 20 to be immunized, this is, in fact, a drawing of two samples from the large guinea pig population. The assumption should be made that the mean length of life of the two groups will not be equal if they are allowed to live and die normally. The error made by many tuberculosis research workers and others is the assumption that the means of samples are equal. This error becomes greater as the sizes of samples become smaller. For example, if a group or sample of 20 male guinea pigs, all three months old, lived to an average of 35 months, the assumption must be made that other exactly similar groups will not have the same mean life-time of 35 months. This statistical principle applies to mean weights of spleen, mean number of nurses infected, or any other characteristic. It may be applied broadly to many researches where conclusions are based on differences between means of samples drawn from a large population.

*Calculation of differences between mean lengths of life of samples of normal guinea pigs:* Although this is the answer to the question asked in the "purpose of this paper," more than this is required in the correct interpretation of an immunity test. This calculation involved two steps: calculation of expectation of life and obtaining results on random sampling of expectation of life.

*Calculation of expectation of life:* The possibility of calculating life tables for the guinea pig is due to the recent publication by Eaton (2) of his studies on the longevity of the guinea pig. Complete life tables based on Eaton's data were calculated by methods described by Dublin and Lotka (3), but are shown here only in part, as table 1. This table tells how long guinea pigs may be expected to live in a normal environment. Thus, in a large group of five-month-old guinea pigs, each will live, on the average, an additional 42 months if they are males, and 24 months if they are females. Since the females have a decidedly lower expectation of life, both virulence and immunity tests will probably be improved by using males only.

The reason for differences in mean expectation of life of samples of guinea pigs can be seen in table 1. In the above group of five-month-old

males, one cannot tell which guinea pig will live an additional month or seventy months. Control and immunized groups will contain unknown proportions of guinea pigs destined to live longer or shorter lives. This is the same as saying that in a group of 10,000 white male children, age two years, each will live, on the average, an additional 59 years. What this average figure will be for this or that random sample of 20 such children will differ from sample to sample. How great might this difference be for a group of 20 and 20 or of 50 and 50 guinea pigs? The answer was calculated from table 1.

TABLE 1

*Expectation of life of normal guinea pigs*

| AGE OF GUINEA PIGS | AVERAGE NUMBER OF MONTHS REMAINING TO EACH GUINEA PIG ALIVE AT BEGINNING OF AGE INTERVAL IN FIRST COLUMN | |
|---|---|---|
| *months* | *males* | *females* |
| 0– 1 | 46 | 27 |
| 5– 6 | 42 | 24 |
| 10–11 | 39 | 22 |
| 15–16 | 35 | 20 |
| 20–21 | 32 | 19 |
| 25–26 | 28 | 17 |
| 30–31 | 26 | 16 |
| 35–36 | 24 | 15 |
| 40–41 | 20 | 14 |
| 45–46 | 16 | 15 |
| 50–51 | 14 | 15 |
| 55–56 | 14 | 13 |
| 60–61 | 12 | 14 |
| 65–66 | 9 | 14 |
| 70–71 | 5 | 13 |
| 75–76 | 1 | 8 |
| 80–81 | 0 | 3 |
| 91–92 | | .5 |

*Results of random sampling of expectation of life:* A hypothetical dealer was asked to send 40 normal male guinea pigs, all 90 days old, to a laboratory where two groups of 20 were formed. One group was "immunized" with sterile salt solution, followed by "infection" of both groups with sterile sugar solution. Both groups were allowed to live in a normal environment until all died. The mean (or average) length of life of the two groups was calculated, and the difference found by simple subtraction. Assuming that 100 such blank immunity tests were made, the following results were calculated by statistical methods

(4) and the aid of the complete guinea-pig life tables. Eaton's longevity data make it unnecessary to actually carry out these blank tests. In 50 tests, immunized groups will outlive their controls. In 34 of the 100 tests, immunized groups will outlive their controls by anywhere from 0 to 6 months mean life after infection. In 16 tests out of 100, the difference in favor of immunized groups will be from 6 to 14 months. The same figures are true for control groups outliving their corresponding immunized groups. These differences are cut down to about one-half of the above when samples of 50 plus 50 guinea pigs make one blank immunity test.

But these differences between mean length of life of groups of guinea pigs are not those needed in the interpretation of actual tests, because none of the above animals were immunized or infected.

*Revised virulence test:* Perhaps the first step in an orderly study of the longevity-immunity test is to make what might be called revised virulence tests by a variation of the above blank immunity tests. As before, convenient groups of guinea pigs are "immunized" with sterile salt solution. But now this is followed by infection of immunized and control groups with moderate doses, 0.000,01 mgm. or less, of virulent human tubercle bacilli, under carefully standardized conditions (1, page 502). As in the blank immunity tests, immunized groups will outlive their controls in 50 per cent of the tests. The differences between mean lengths of life, however, cannot be calculated. They must be found experimentally. Let it be assumed provisionally that the differences range from 0 to 6 months in most of the virulence tests. This will furnish a sounder basis for judging the potency of an immunizing material. Knowing that immunized groups may outlive their controls by as much as 6 months, when salt solution is the immunizing agent, potency will not be assumed from one test, unless the immunized group outlives its control by more than the blank differences.

*Criterion of success:* If in five actual immunity tests immunized groups outlived their controls in all five tests, even by a small margin, the probability is that immunization actually occurred. This becomes a practical certainty if it happened in ten tests.

## SUMMARY

1. It is practically impossible to select two or more small groups of guinea pigs so that the groups will have the same mean length of life. As ordinarily carried out, on the erroneous assumption that mean lengths

of life of guinea pig samples are equal, the longevity-immunity test is worse than useless because it confounds research workers.

2. In blank immunity tests, with sterile salt solution for immunization and sterile sugar solution for infection, immunized groups will outlive their controls in one-half the tests, and frequently by as much as 6 months.

3. A revised virulence test, better adapted to the needs of immunity testing, is suggested.

4. Only male guinea pigs should be used in virulence and immunity tests.

The writer is glad to acknowledge his indebtedness to Dr. John R. Mohler, Chief of the Bureau of Animal Industry, Washington, D. C., for permission to use data in Bureau publications, and to Dr. O. N. Eaton, also of the Bureau, for many helpful suggestions.

## BIBLIOGRAPHY

(1) Berg, W. N.: Tubercle, 1936, *17*, 496.
(2) Eaton, O. N.: Jour. Exp. Zool., 1932, *63*, 261.
(3) Dublin, L. I., and Lotka, A. J.: Length of life, Ronald Press, New York City, 1936.
(4) Camp, B. H.: The mathematical part of elementary statistics, D. C. Heath & Co., New York City, 1934, p. 267.

# DAILY VARIATIONS IN THE TUBERCULIN REACTION[1, 2]

## 1. The Range of Variation in Tuberculous and Control Subjects

JOHN S. HOWE

Since Robert Koch (1), in 1890, first reported the use of tuberculin, a vast and highly controversial literature has accumulated on the subject of allergy in tuberculosis. Pirquet (2) recognized clearly certain discrepancies and variations in the cutaneous reaction to tuberculin. In particular he recognized the "cachectic reaction," the weak or negative reaction to tuberculin which may occur in cachexia, miliary tuberculosis, tuberculous meningitis, and in certain infectious diseases, particularly measles. These variations in the tuberculin reaction are now generally accepted and explained either as the result of desensitization or of failure of reactivity associated with marked dehydration.

Rich (3) has performed tuberculin tests at intervals of several days in patients with miliary tuberculosis, and states that these reactions show marked variations, which he suggests may be due to desensitization by large numbers of tubercle bacilli entering the blood-stream. Gernez and Marchandise (4) stress the importance of nonspecific factors in determining the variations in intensity of skin reactions to tuberculin, particularly vasomotor and circulatory factors. They demonstrated local differences in the tuberculin reaction, done bilaterally on cases of hemiplegia and of peripheral vascular disease.

Roberts (5) has reviewed the subject of variations in tuberculin allergy. He stresses particularly the occurrence of transient negative reactions to tuberculin in positive reactors, which he considers may be due to acquired tolerance to tuberculin, anergy in advanced tuberculosis, or nonspecific factors. Hamburger (6), Peyrer (7), and Schnippenkötter (8) in separate contributions have described the occurrence of seasonal trends in the tuberculin reaction, the first two authors in children, and the last in adults with tertiary tuberculosis. In general they agree on

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] From the Department of Pathology, University of Illinois, College of Medicine, Chicago, Illinois.

a late spring peak in sensitivity to tuberculin, with smaller reactions in the summer and winter months. All their conclusions were based on tuberculin tests done at intervals of one month or more.

Ossoinig (9) noted a seasonal trend in the tuberculin reaction in children examined repeatedly over a period of three years, as well as periodic variations in skin sensitiveness, with a positive phase lasting one week, and a negative phase lasting from one to three weeks. He performed daily tuberculin reactions on a series of fifteen children for two-week periods, at intervals of several weeks. In these, he noted the parallel trend of the tuberculin reaction in different individuals on the same day, which he was unable to explain, although he suggested that meteorological factors must play a rôle.

With the exception of the work of Ossoinig, there are no reported studies of the tuberculin reaction based on tests done at short regular intervals. All of the observations and attempted correlations are based on single tuberculin reactions performed at intervals of several weeks or more. This series of observations was undertaken in the hope that a careful study of the tuberculin reaction, using daily tests over as long a period as practicable, might clear up some of the discrepancies.

## METHODS

Recently von Gröer (10) has described a method using simultaneously two different dilutions of tuberculin injected intracutaneously into the back, at intervals of four to six weeks. The average diameter of the reactions was measured, and multiplied by the negative logarithm of the dilution of tuberculin to obtain a product characteristic for the reaction and the dose. He found that the reactions were roughly proportional to the negative logarithm of dilution, and classified tuberculosis in children on the basis of variations from this mathematical ratio, which he believes to be of prognostic significance.

Our method was adapted from that of von Gröer, with certain modifications. The subjects were four adults with pulmonary tuberculosis and two adult control subjects with positive tuberculin reactions but negative X-ray and clinical evidence for tuberculosis.

In order to have a standard tuberculin with comparable results over the entire period, Purified Protein Derivative Tuberculin (Long and Seibert (11)) was used. Accurate dilutions were made fresh daily from a stock solution, kindly furnished by the Phipps Institute, through the courtesy of Doctor Long and Doctor Seibert. In 5 of the 6 subjects,

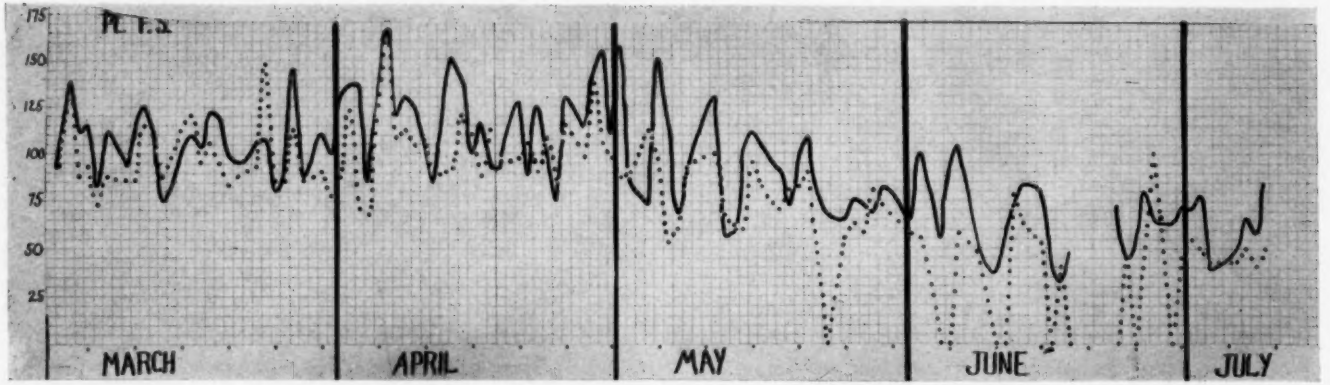



FIG. 1. Tuberculin curve for patient 1 (*F. S.*). For discussion see text

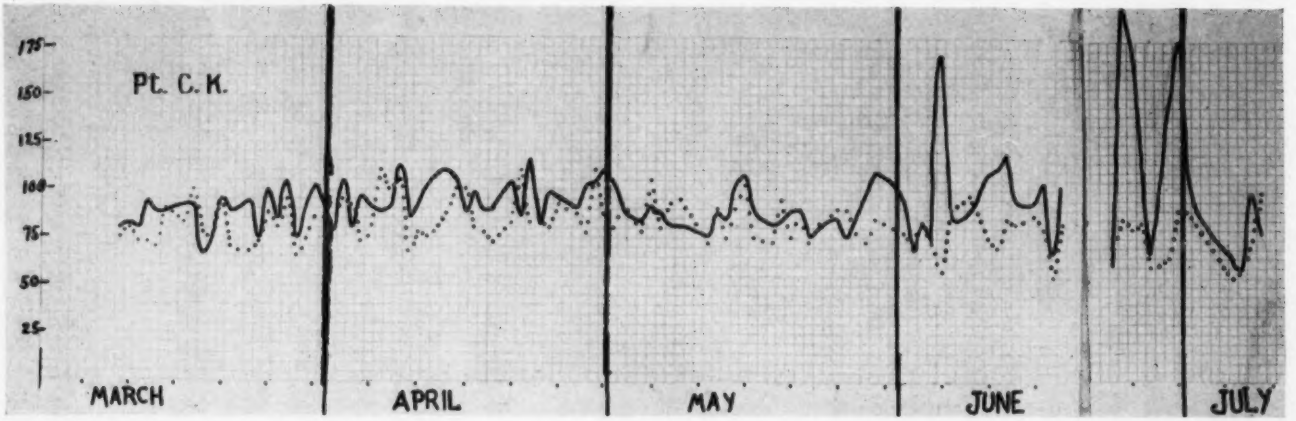



FIG. 2. Tuberculin curve for patient 2 (*C. K.*). This is plotted to the same scale and covers the same period of observation as the chart for patient 1. The solid line represents the reaction to the larger dose of .000,1 mgm. P.P.D. and the dotted line the reaction to the smaller dose of .000,01 mgm. For further discussion see text.

the doses used were .000,1 and .000,01 mgm. of P.P.D. In one subject it was necessary to use larger doses of .001 and .000,1 mgm. to obtain easily measured reactions.

The two doses were simultaneously injected intracutaneously in the back and the reactions read twenty-four hours after injection, when the average diameter of the sharply defined zone of erythema was recorded. These average diameters, multiplied by the negative logarithm of the corresponding dose of P.P.D. in mgm., give the von Gröer product for each reaction. These products, plotted on a graph of which the baseline is the date of injection, give a graphic record of the daily level and course of allergy in each subject (figure 1).

At the same time various clinical, chemical, serological and haematological observations were made daily and charted so that any correlations might be analyzed. These observations included the blood-pressure, pulse, respirations, leucocyte and differential counts, temperature, weight, sputum volume, clinical notes, blood pH and $CO_2$ content, cholesterol, methylene-blue reduction time, etc.

## RESULTS

The tuberculin curves for the four patients and two control subjects are given in figures 1 to 7. The periods of continuous observation vary from 1 to 6 months, and the longest period of observation on any one subject with interruptions is 12 months.

Figure 1 shows the curve for patient 1 (*F. S.*), a Mexican male of 51 years, with a diagnosis of far advanced bilateral pulmonary tuberculosis with cavitation. The period of observation extended from March 2 to July 9, 1936. The patient died August 11, 1936. The reaction to the larger dose of P.P.D. (.000,1 mgm.) is represented by the solid line; the reaction to the smaller dose (.000,01 mgm.) by the dotted line. The numbers at the left margin of the graph are the von Gröer products and the baseline is the date of injection, each small square representing one day.

Obviously this patient shows a marked cyclical variation in the reaction to the same doses of tuberculin, the cycles extending over periods from one to several days. From the first week of May, the curve shows a gradual decline to the end of observations in July. On May 23 and on June 4, 5, 10, 11, 16, 18, 23, 25 and 30 the reaction to the smaller dose of tuberculin is entirely negative, while the reaction to the larger dose is decreased. If the variability of the reaction be expressed as a per cent of the maximal reaction to the doses used, we have here a 100 per cent variability in the tuberculin reaction. The gradual decline in the level of allergy from the first of May to July may repre-

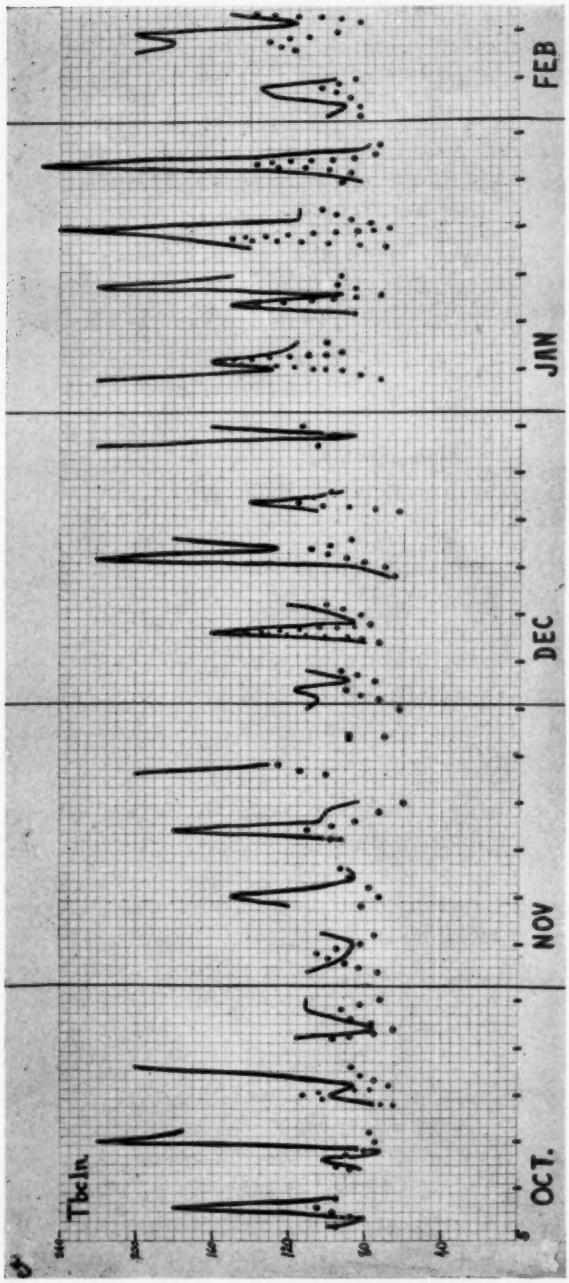



FIG. 3. Another tuberculin curve for patient 2 (*C. K.*). This is plotted to the same scale and the doses of P.P.D. are the same as in fig. 2. For further discussion see text.

sent an actual seasonal trend in sensitivity to tuberculin, such as has been reported by Peyrer (7), or it may represent increasing failure to react ("anergy") in a moribund patient.

Patient 2 (*C. K.*) is a white male of 48 years, a machinist, diagnosed silicosis and pulmonary tuberculosis, moderately advanced. This patient shows few signs of tuberculous activity, and his lesions are essentially of the chronic

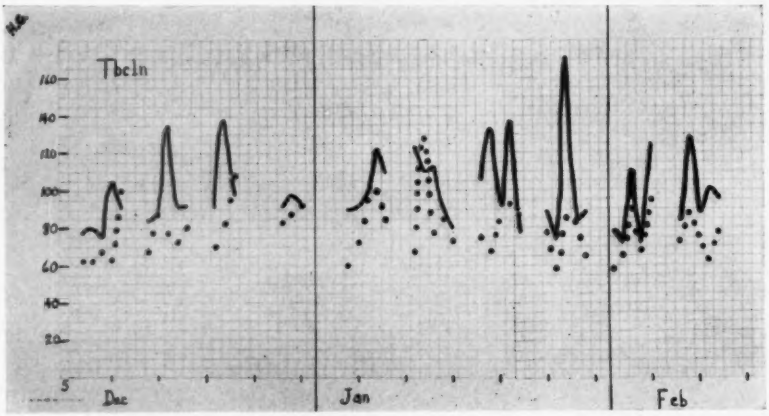



FIG. 4. Tuberculin curve for patient 3 (*H. G.*). Plotted to the same scale and using the same doses as in the preceding charts, the solid line again representing the reaction to the larger dose of P.P.D. For discussion see text.

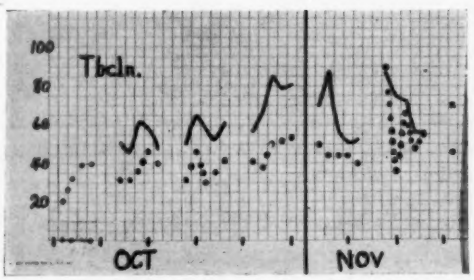



FIG. 5. Tuberculin curve for patient 4 (*W. K.*). For discussion see text

fibroid type, with symptoms of dyspnoea, dry cough, chiefly referable to his reduced pulmonary capacity.

Two tuberculin curves for this patient are shown. The first (figure 2) covers the period from March to July, 1936. This curve shows a generally lower level of tuberculin allergy than in patient 1, with the cyclical variations present but less marked. On June 5, 24, 25 and 30 there are exaggerated reactions followed by a return to the usual level.

The second chart for this patient (figure 3) covering the period from October, 1936 to February, 1937 shows a higher level of allergy and extreme fluctuations in the level of allergy reaching a peak in the latter half of January, 1937. In each of these curves the variability of the reaction is 70 per cent of the maximal reaction to the doses used.

Patient 3 (*H. G.*) (figure 4) is a white male of 38 years, diagnosed pulmonary tuberculosis with cavitation, classified as moderately advanced. The period of observation was from December, 1936 to February, 1937. The curve shows a fairly high level of allergy, reaching a peak in the last week of January, 1937,

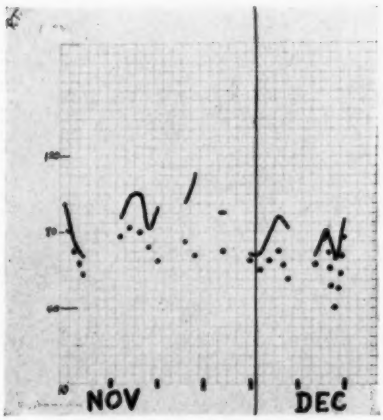



FIG. 6

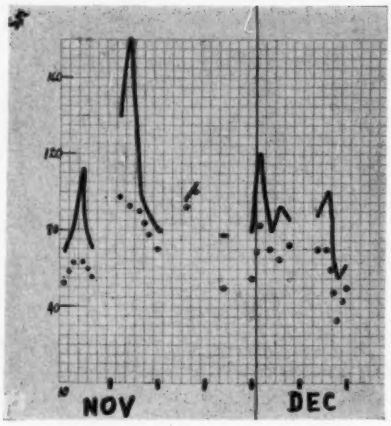



FIG. 7

FIG. 6. Tuberculin curve for control subject 1 (*R. T.*). The solid line represents the reaction to the larger dose of .000,1 mgm. and the dotted line the reaction to the smaller dose of .000,01 mgm. P.P.D. For discussion see text.

FIG. 7. Tuberculin curve for control subject 2 (*S. M.*). The solid line represents the reaction to the larger dose of .000,1 mgm. and the dotted line the reaction to the smaller dose of .000,01 mgm. P.P.D. For discussion see text.

followed by a drop in February. The daily fluctuations are marked. The variability is 60 per cent of the maximal reaction to the doses used.

Patient 4 (*W. K.*) (figure 5) is a white male of 23 years, diagnosed pulmonary tuberculosis with cavitation, far advanced. He had a rapidly progressive tuberculous pneumonia with duration of six months from first symptoms to death. The tuberculin record covers only October and part of November, 1936. With this patient it was necessary to use a larger dose of tuberculin to obtain easily measured reactions, namely .001 mgm. and .000,1 mgm. of P.P.D. Again the solid line represents the larger dose .001 mgm. Even with these larger doses, the level of the reaction as charted is relatively low,

but the same cyclical variations are present as in the other subjects. The variability is 50 per cent of the maximal reaction. It is interesting that a relatively high level of allergy is maintained up to the last observation, which was made on the day preceding death. This is contrary to the generally accepted loss or depression of allergy ("anergy") in moribund patients.

Control subject 1 (*R. T.*) is a white male of 28 years, a laboratory technician, without X-ray evidence of active tuberculosis. The tuberculin reactions (figure 6) cover a period in November and December, 1936. The general level of allergy is comparable to that of the first three patients, and the same cyclical variations in the tuberculin reactions are present. The variability is 50 per cent of the maximal reaction to the doses used.

Control subject 2 (figure 7) is a white male of 35 years, a laboratory technician, with X-ray and clinical examination negative for active tuberculosis. The period of observation covers part of November and December, 1936. The level of allergy in general is higher than that of control subject 1, and the fluctuations are more marked. The variability is 60 per cent of the maximal reaction to the doses used.

## SUMMARY AND CONCLUSIONS

1. A method adapted from von Gröer is presented for performing daily tuberculin tests and recording the results graphically to give a curve of allergy.

2. Curves of allergy are presented for four patients with pulmonary tuberculosis and two control subjects with positive reactions to tuberculin but no X-ray or clinical evidence of tuberculosis.

3. The tuberculin reactions, in both subjects and controls, show marked daily fluctuations varying from 100 per cent to 50 per cent of the maximal reactions to the doses used.

4. A possible example of a seasonal trend in the reaction to tuberculin is presented in patient 1.

5. Patient 4 presents an example of a moderate reaction to tuberculin in a moribund patient sustained to the day preceding death.

6. In this short series, there are no apparent differences in the tuberculin curves of tuberculous patients and control subjects, with the possible exception of patient 4, who was definitely less sensitive to tuberculin than the other subjects and required larger doses to produce an easily measured reaction.

7. The extent of the daily variations in the tuberculin reactions suggests the necessity of caution in drawing conclusions, or in making clinical correlations, from single tuberculin reactions at long intervals.

## REFERENCES

(1) Koch, R.: Weitere Mittheilungen über ein Heilmittel gegen Tuberkulose, Deutsche med. Wchnschr., 1890, *16*, 1029.

(2) Pirquet: Allergie, Berlin, Julius Springer, 1910.

(3) Rich, A. R., and McCordock, H. A.: Rôle of allergy, immunity, and other factors in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, *44*, 273.

(4) Gernez, C., and Marchandise, C.: Action de certains facteurs non-spécifiques sur l'intensité de la cutiréaction tuberculinique, Compt. rend. Soc. biol., 1935, *118*, 996.

(5) Roberts, E. F.: Variations in tuberculin allergy, Yale J. Biol. & Med., 1930, *2*, 341.

(6) Hamburger, F.: Jahreszeitliche Schwankungen der Tuberkulinempfindlichkeit, Münchn. med. Wchnschr., 1920, *67*, 398.

(7) Peyrer, K.: Jahreszeitliche Schwankungen der Tuberkulinempfindlichkeit und mancher Tuberkuloseerkrankungen, Beitr. z. Klin. d. Tuberk., 1921, *48*, 137.

(8) Schnippenkötter, W.: Laufende Allergieprüfungen während längeren Heilstättenaufenthaltes bei meist tertiären Tuberkulosen und jahreszeitliche Schwankungen der Tuberkulinempfindlichkeit, Beitr. z. Klin. d. Tuberk., 1926, *65*, 41.

(9) Ossoinig, K.: Über Schwankungen der Tuberkulinempfindlichkeit, Ibid., 1926, *64*, 652.

(10) von Gröer, F.: New possibilities of a prognostic diagnosis of tuberculosis in children, Jour. Pediat., 1935, *6*, 297.

von Gröer, F., *et al.*: Tuberkulosestudien, I, II, III and IV, Zeitschr. f. Kinderh., 1934, *56*, 379, 390, 631, 669.

(11) Long, E. R., Seibert, F., *et al.*: Tuberculin surveys with Purified Protein Derivative. Determination of optimum dosage, Amer. Rev. Tuberc., 1934, *30*, 733.
Purified Protein Derivative as a standard tuberculin, Ibid., 1934, *30*, 757.

# DAILY VARIATIONS IN THE TUBERCULIN REACTION[1, 2]

## 2. Relation to the Vascular Pressor Episode

JOHN S. HOWE

In a preceding paper (1) we have presented curves of allergy for four patients with clinical pulmonary tuberculosis and two control subjects with positive reactions to tuberculin but no evidence of active tuberculosis. A striking feature of all these curves of allergy is the marked cyclical variation in the reaction to the same doses of tuberculin over a period of one to several days. In an attempt to explain these variations, the tuberculin curves were analyzed in relation to other observations made daily and in relation to the meteorological environment.

Figure 1 is a typical composite chart showing the more important daily observations on patient 2 (*C. K.*) for the months of March and April, 1936. Beginning at the top, the numbered curves represent the following:

(*1*) Meteorograph for Chicago. The heavy line represents the barometric pressure and the dotted line the daily mean temperature.
(*2*) Percentage of immature leucocytes in the circulating blood.
(*3*) Percentage of polymorphonuclear leucocytes.
(*4*) Percentage of eosinophiles, one black square equals one per cent.
(*5*) Leucocyte count expressed in units of 1,000.
(*6*) Methylene-blue reduction time, that is, the time in hours required to reduce to a colorless solution .01 cc. of a 1 to 1,000 solution of methylthionine chloride, USP, injected intracutaneously. This is a measure of tissue oxidation.
(*7*) Respiratory rate taken daily at the same hour under basal conditions.
(*8*) The heavy black curve represents the daily systolic and diastolic blood-pressure levels, and the light line represents the pulse rate.
(*9*) Carbon dioxide content of the venous blood in volumes per cent.
(*10*) pH of the venous blood.
(*11*) Blood cholesterol in milligrams per cent.

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] From the Department of Pathology, University of Illinois, College of Medicine, Chicago, Illinois.

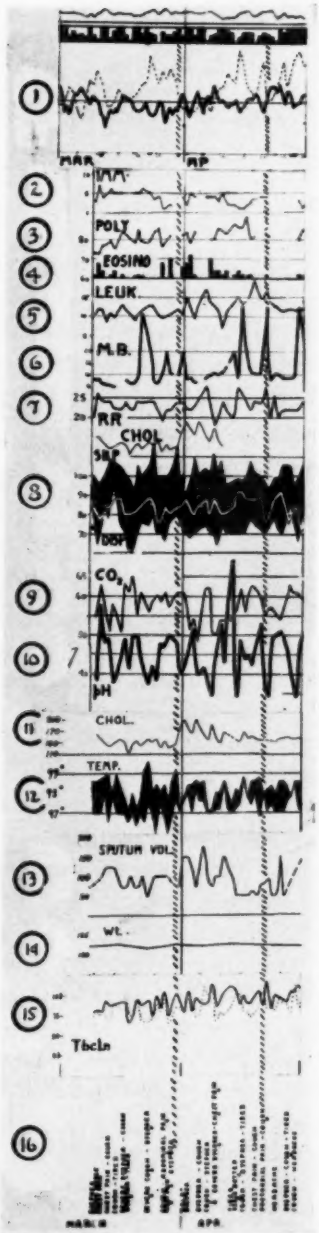



FIG. 1. Comprehensive chart for patient 2 (*C. K.*). For discussion see text

(*12*) Daily minimum and maximum temperatures.
(*13*) The 24-hour sputum volume in cc.
(*14*) Weight of the patient. This was taken only at weekly intervals.
(*15*) Tuberculin curve, the reaction to two simultaneous doses of P.P.D. expressed as the von Gröer product.
(*16*) Daily clinical notes and symptoms.

On this composite chart only two episodes out of several have been diagonally shaded to indicate the correlations. The first episode which has been shaded occurs on March 30, a day characterized by unstable meteorological conditions with a rapidly falling temperature, a sharply rising barometric pressure and slight precipitation, all characteristic of an infall of polar air. In curve 5, this is seen to correspond to an increased reaction to tuberculin, which is associated with a systolic and diastolic blood-pressure peak (curve 8) and a temperature peak of 99.2°F. Associated with these findings, there is a moderate leucocytosis with an increase in the percentage of polymorphonuclears and immature leucocytes, and a slight increase in the respiratory rate. The blood chemistry shows a high carbon dioxide content and a relatively high pH, which starts to fall sharply to a lower level on the next day. The clinical notes for this episode reveal complaints of chest pain and dyspnoea on the two preceding days, that is, at the beginning of the polar infall when peripheral vascular spasm, reflected in a rising diastolic pressure, had caused an anoxaemia, which was reflected clinically in this patient with reduced pulmonary capacity (silicosis and tuberculosis) by pain in the chest and dyspnoea.

The second shaded episode on the comprehensive graph occurs on April 21, 1936. This period, as shown in the meteorograph (curve 1, figure 1), is characterized by a very rapidly falling temperature and a sharply rising barometric pressure, with slight precipitation, again characteristic of an infall of polar air. The tuberculin curve (curve 15) shows a double peak with the greatest exaggeration of the reaction on the succeeding day, April 22. The clinical reflection (curve 16) consists of precordial pain and increased cough. The sputum volume (curve 13) shows a double peak quite similar to the tuberculin reaction. The blood-pressure (curve 8) shows a delayed fall in the systolic and diastolic pressures, though this effect is not as clear-cut as in the preceding episode. The blood picture shows a marked leucocytosis (17,000) with 1 per cent eosinophiles and a high percentage of polymorphonuclear and immature leucocytes. The methylene-blue reduction time is greatly prolonged (increased tissue oxidation) concurrent with an increased respiratory rate. The carbon dioxide content of the blood is low as is also the blood pH. The temperature and blood cholesterol show no marked change in this episode.

This preliminary consideration of a typical comprehensive chart illustrates the fact that, despite the complexity, there is a trend of

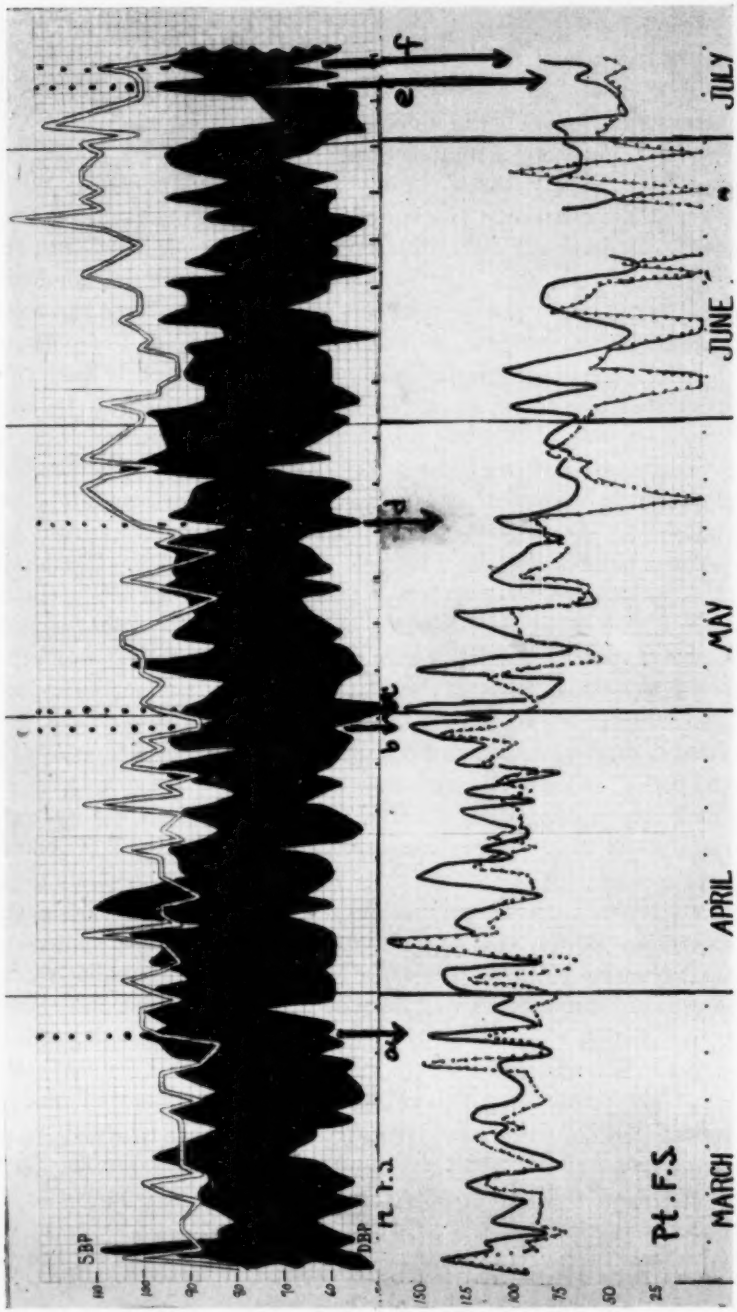



FIG. 2. Comparison of tuberculin and blood-pressure curves for patient 1 (*F. S.*) from March to July, 1936. For discussion see text

correlation in all the observations, clinical, chemical and serological. We shall limit this paper to a detailed consideration of the relation between the tuberculin curves and the diastolic blood-pressure, taken daily at the same time under basal conditions. The diastolic blood-pressure may be considered a fairly rough measure of vascular permeability, since a dilated arteriole is more permeable than a constricted one, as has been shown in many studies on inflammation by Cohnheim (2), as well as others. Also the anoxaemia caused by prolonged vascular spasm may increase the permeability of the capillary endothelium, as has been pointed out by Burrows (3).

Petersen (4) has shown the close correlation between the meteorological environment and the rhythm of vascular spasm and dilation, as measured by the blood-pressure readings taken daily. For simplification we will omit the meteorograph and compare the blood-pressure and tuberculin curves in our six subjects:

Figure 2 shows in the upper solid black curve, the daily systolic (upper limit of curve) and diastolic (lower limit) blood-pressure levels. The double light line represents the pulse rate taken at the same hour daily. The lower curve represents the daily reaction to two doses of tuberculin; the solid line, the reaction to the larger dose of .000,1 mgm. P.P.D., and the dotted line the reaction to the smaller dose of .000,01 mgm. P.P.D.

An analysis of the tuberculin curve shows 37 distinct peaks of increased sensitivity to tuberculin. If these are compared with the diastolic blood-pressure curve for the same days, 87 per cent of these peaks are synchronous with a falling diastolic pressure following a distinct pressor episode, that is, with relaxing vascular spasm and the attendant increase in vascular permeability. Several examples of these episodes are indicated by the arrows a, b, c, d, e and f.

Applying the same method to the periods of decreased sensitivity to tuberculin, we have 10 days in May and June when the reaction to the smaller dose of tuberculin was entirely negative. Eight of these ten episodes are clearly synchronous with increasing diastolic blood-pressure and the attendant decreased vascular permeability associated with vascular spasm.

Figures 3 and 4 show similar curves for two different periods of observation on patient 2 (*C. K.*), diagnosed as silicosis and moderately advanced pulmonary tuberculosis. The first tuberculin curve shows 35 peaks of tuberculin sensitivity of which 77 per cent are clearly associated with a falling diastolic pressure following a pressor peak. The second graph for this patient (figure 4, October, 1936 to March, 1937) shows 30 distinct peaks of tuberculin sensitivity, of

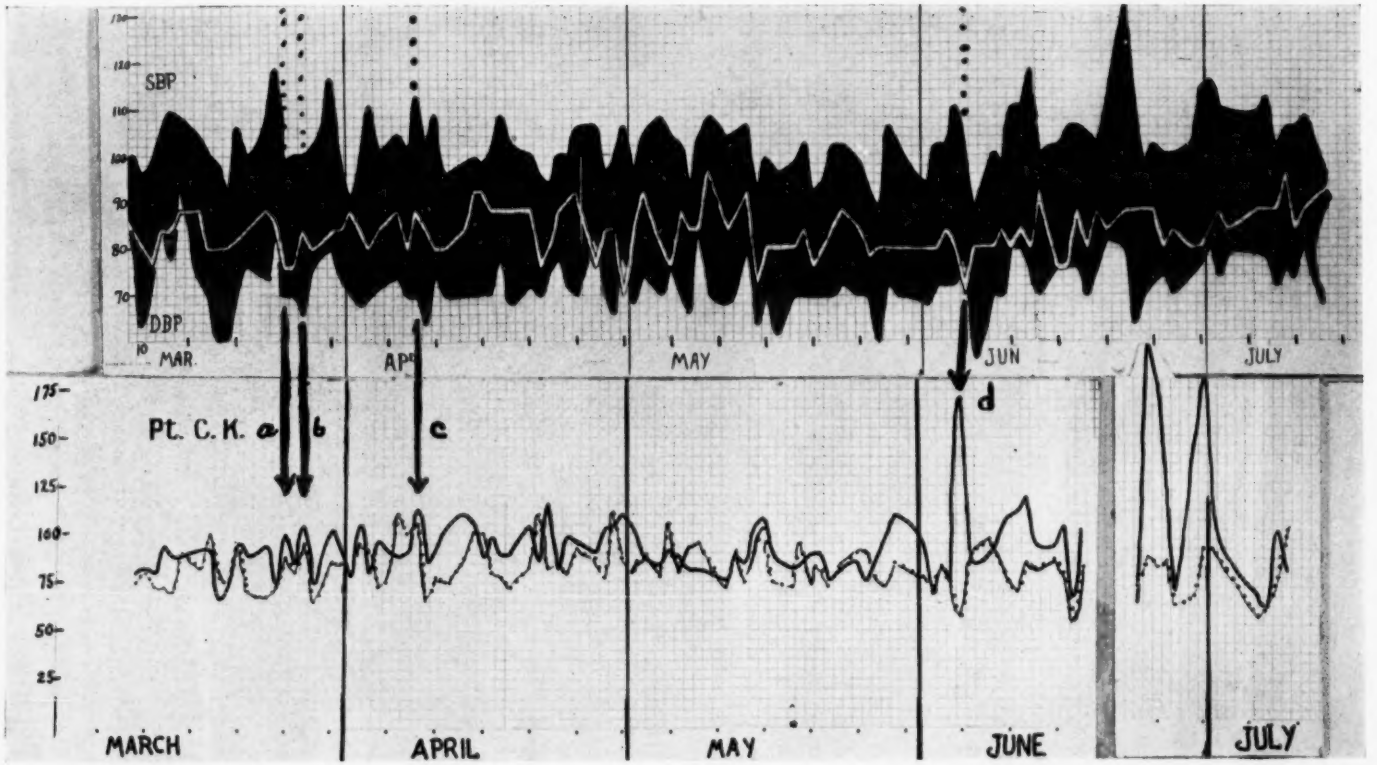



FIG. 3. Comparison of blood-pressure and tuberculin curves for patient 2 (*C. K.*) from March to July, 1936. Again the lower limit of the solid black area represents the diastolic pressure, and the lower curve shows the reactions to two doses of tuberculin, the solid line to .000,1 mgm. and the dotted line to .000,01 mgm. P.P.D. For discussion see text.

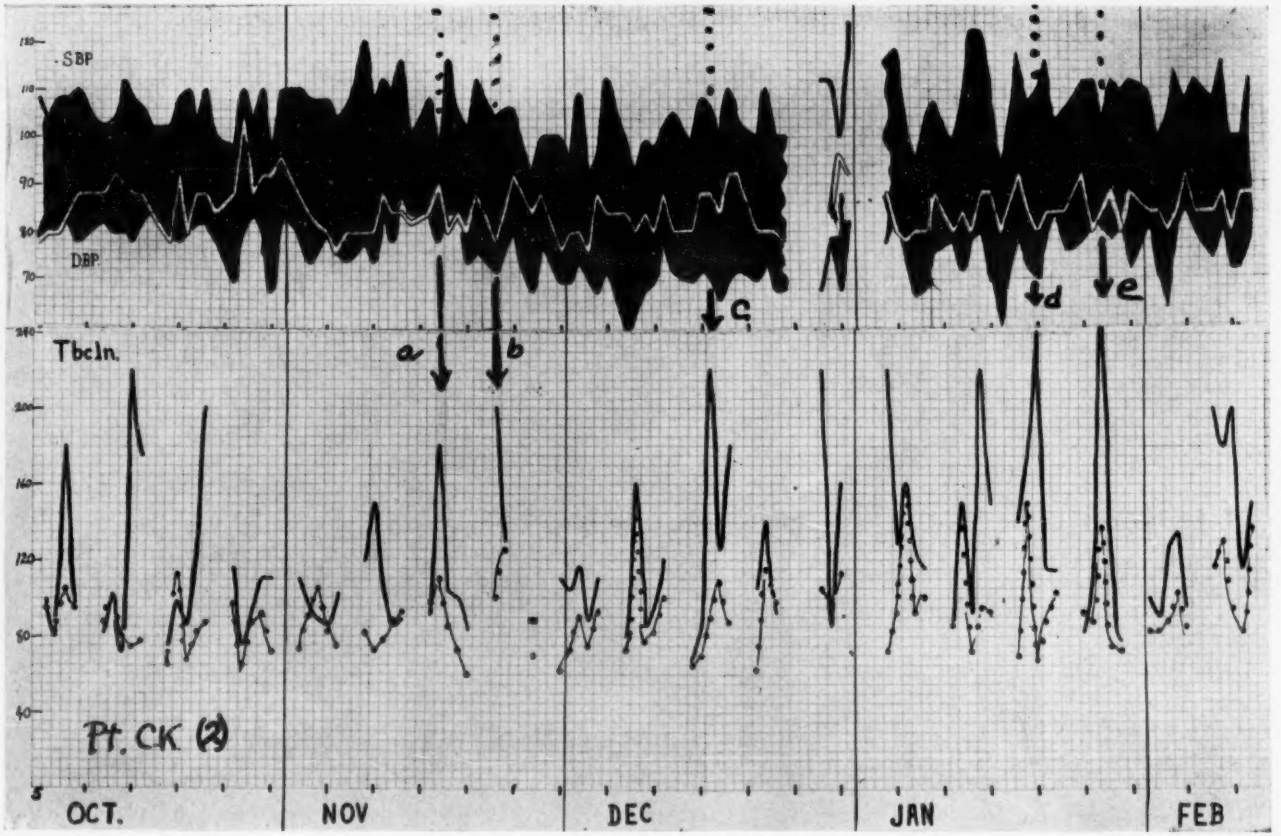



FIG. 4. Comparison of blood-pressure and tuberculin curves for patient 2 (*C. K.*) from October, 1936 to February, 1937. The schema is the same as in fig. 3. For discussion see text.

which 83 per cent are correlated with a falling diastolic pressure. Typical examples are indicated by arrows a, b, c and d in both charts.

Figure 5 shows the curve for patient 3 (*H. G.*), diagnosed as moderately advanced pulmonary tuberculosis with cavitation. The tuberculin curve shows 14 distinct peaks of tuberculin sensitivity of which 78 per cent are correlated

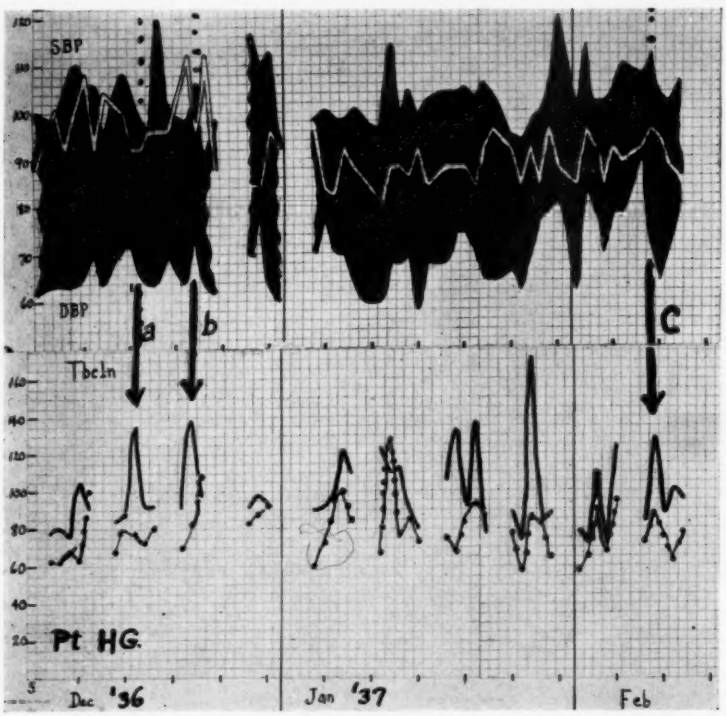



FIG. 5. Comparison of blood-pressure and tuberculin curves for patient 3 (*H. G.*) from December, 1936 to February, 1937. The schema is the same as in the preceding figures. For discussion see text.

with falling diastolic pressures. Episodes a, b and c, indicated by arrows, are examples.

Figure 6 shows a similar curve for patient 4 (*W. K.*), a case of tuberculous pneumonia with death six months after onset of symptoms. The tuberculin curve shows 10 peaks of sensitivity, of which 90 per cent are correlated with falling diastolic pressure.

Figure 7, showing the curve for control subject 1, also shows 6 peaks of tuberculin sensitivity, of which 5 or 83 per cent are correlated with a falling diastolic pressure.

Figure 8 shows the curves for control subject 2. The tuberculin curve shows 6 peaks of tuberculin sensitivity, 100 per cent correlated with a falling diastolic pressure. Examples of individual episodes are indicated by arrows a, b and c.

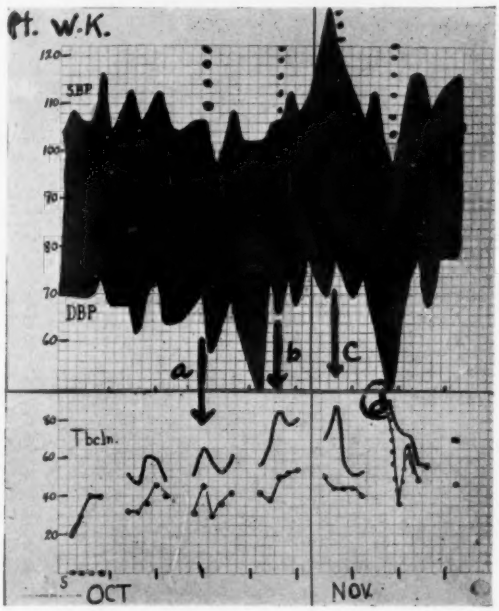



FIG. 6. Comparison of blood-pressure and tuberculin curves for patient 4 (*W. K.*) for October and November, 1936. The upper solid black area represents the systolic (SBP) and diastolic blood-pressures. The lower curve represents the von Gröer products for the reaction to the tuberculin. In this case it was necessary to use larger doses; the solid line is the reaction to the larger dose of .001 mgm. and the dotted line the reaction to the smaller dose of .000,1 mgm. P.P.D. There are 10 well defined episodes of increased sensitivity to tuberculin of which 9, or 90 per cent, are associated with a falling diastolic pressure. The arrows a, b, c and d indicate examples.

Finally, a comparison of the tuberculin curve of different subjects observed over the same period, shows a striking tendency for the peaks of tuberculin sensitivity to be synchronous, and the form of the curves to be roughly similar. Figure 9 shows segments of the tuberculin curves for 4 subjects (two patients and two controls) for a period in December, 1936, which happens to be the

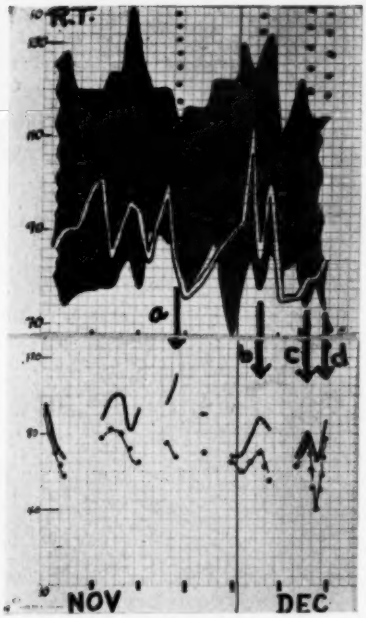



FIG. 7. Comparison of blood-pressure and tuberculin curves for control subject 1 for November and December, 1936. The schema is the same as for preceding figures. For discussion see text.

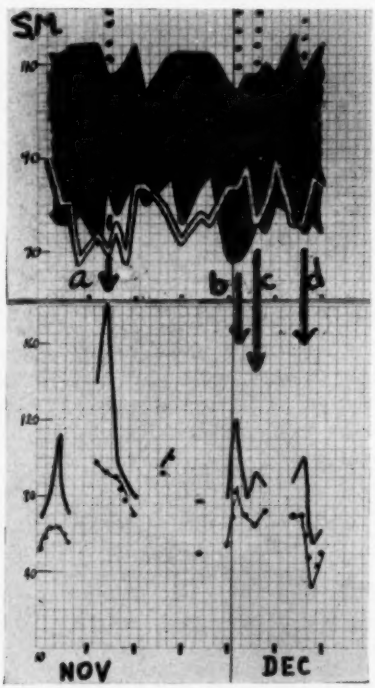



FIG. 8. Comparison of blood-pressure and tuberculin curves for control subject 2 for November and December, 1936. The schema is the same as for preceding figures. For discussion see text.

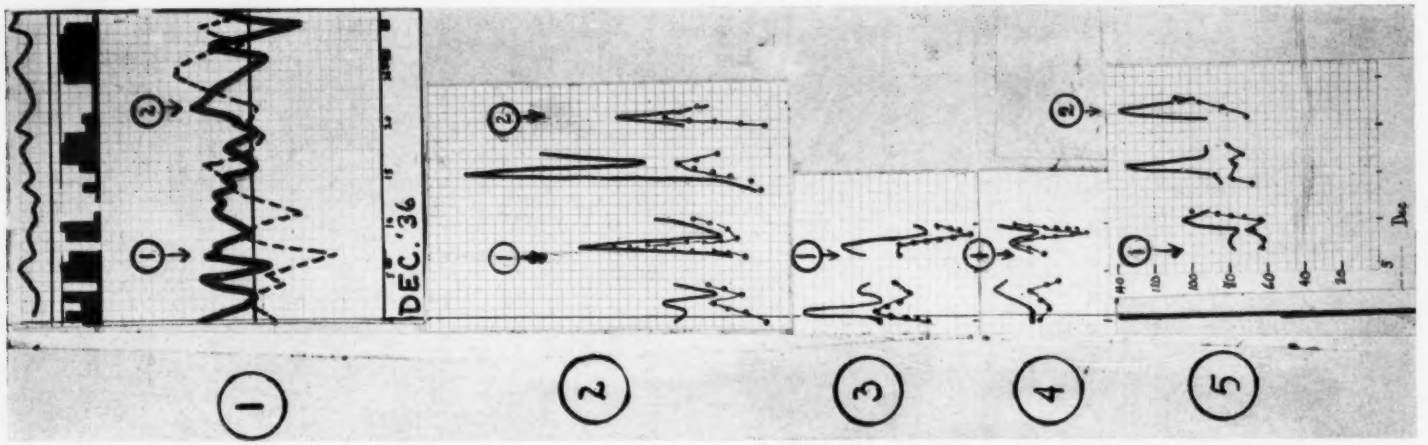



FIG. 9. Comparison of tuberculin curves for two patients and two control subjects for December, 1936, with superimposed meteorograph. The circled 1 and arrow indicate an increased reaction to tuberculin occurring on the same day in all four subjects, and corresponding to a barometric peak on the meteorograph (heavy line in curve 1 represents the barometric pressure). The similarity of the tuberculin curve for this entire week in all subjects is striking. Arrow 2 indicates a similar peak in the tuberculin curve for patients 2 and 3, again corresponding to a barometric peak in curve 1.

only period when observations were made simultaneously on this number of subjects. A meteorograph for the period of observation is superimposed. The first episode marked by an arrow is a sharp polar infall on December 6 and 7. This is followed in all 4 subjects by a peak in tuberculin sensitivity one day later, on December 8. The form of the tuberculin curve for this week in all four subjects is strikingly similar.

The other episode of increased sensitivity to tuberculin in subjects 1 and 4, indicated by an arrow, is on December 22 and corresponds to a barometric crest following a sharp polar infall.

## SUMMARY AND CONCLUSIONS

1. There is a definite correlation between the quantitative variations in the tuberculin reaction and the state of the peripheral vessels as measured by daily diastolic blood-pressure levels. In this series of six subjects the correlation ranges from 77 per cent to 100 per cent.

2. Periods of peripheral vasoconstriction, characterized by increasing diastolic blood-pressure, are accompanied by a decreased reaction to tuberculin, and in several instances by completely negative reactions to the smaller dose of tuberculin.

3. Periods of peripheral vasodilation, characterized by a falling diastolic blood-pressure following a definite pressor peak, are accompanied by increased reaction to tuberculin. This exaggeration of the tuberculin reaction is most marked immediately following a marked pressor episode, and may subside with complete vasodilation.

4. In all subjects studied over the same period, the trend of the tuberculin reaction at the same time is roughly parallel; that is, the "peaks and troughs" of the curves for the different subjects coincide more or less closely. This is in accord with the work of Petersen (4), who has shown that vasoconstriction and vasodilation, reflected in the blood-pressure readings, are largely influenced by the meteorological environment, particularly by the infall of polar air, which causes peripheral vasoconstriction, and is reflected as the "pressor episode."

5. The mechanism of these variations in the tuberculin reaction appears to be one of periodic changes in vascular and tissue permeability, affecting the extent of local exudation in response to a definite dose of tuberculin. The increased permeability may also result in an actually increased sensitivity of the cells to tuberculin.

6. The vascular pressor episode may be reflected not alone in variations in the tuberculin reaction but also in clinical symptoms and chemical and

serological changes. The detailed treatment of these must be reserved for a later paper.

## REFERENCES

(1) Howe, J. S.: Amer. Rev. Tuberc., 1938, *37*, 264.
(2) Cohnheim, J.: Lectures on general pathology (English translation), New Sydenham Society, London, 1889.
(3) Burrows, H.: Some factors in the localization of disease, William Wood and Co., New York, 1933.
(4) Petersen, W. F.: The patient and the weather, vols. *I* to *IV*, Edwards Bros., Ann Arbor, 1937.

# THE POSSIBILITY OF SENSITIZATION TO TUBERCULIN[1, 2]

WALDO E. NELSON, A. GRAEME MITCHELL AND ESTELLE W. BROWN

The question whether tuberculin may have sufficient antigenic capacity to induce hypersensitivity to itself has been raised on numerous occasions. If this were the case, the value of tuberculin in the detection of tuberculous infection would be limited to the results of a single injection.

It is well known that sensitization to the tubercle bacillus varies in degree in different persons as well as in the same person at different times, and that comparatively large amounts of tuberculin are sometimes required to elicit a reaction. It has been shown that acute infections (1), ultraviolet irradiation and other factors may temporarily depress tuberculin hypersensitivity and also that there is a depression of allergy in the terminal stage of tuberculosis (2). The work of Johnston (3) indicates that allergy induced by the primary invasion of the tubercle bacillus in the human host tends to follow the course of the infection. The greatest response to tuberculin is obtained during the height of the lymph node involvement and decreases as healing ensues. Stewart's (4) observation that smaller tuberculin reactions occur in adults than in children when the same dosage is employed lends support to this theory. In view of these observations, one naturally wonders to what degree these and other factors may diminish allergic response. It has been stated that it may disappear entirely. Whether this is true or whether the allergic response is simply lower than the level elicited by the maximum amounts of tuberculin ordinarily used for skin testing is an unanswered question.

Sensitization of nontuberculous guinea pigs to an aqueous extract of the tubercle bacillus was demonstrated by Baldwin (5) and by Krause (6). However, attempts to sensitize to Old Tuberculin have not been

[1] From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.

[2] Presented in abstract before the American Pediatric Society, Hot Springs, Virginia, April 30, 1937.

uniformly successful. In the studies in which sensitization has been reported it would appear that it has been due to substances in the culture media (7, 8) and not to the products of the tubercle bacillus itself. A brief review of the literature on this subject is to be found in an article by Aronson and Nicholas (9).

With the introduction of purified tubercle bacillus protein (T.P.T. (10) and MA-100 (11)) for tuberculin testing, the possibility that tuberculin-induced tuberculin hypersensitivity might occur was again suggested. Aronson and Nicholas (9), on retesting a group of children who had failed to react three months previously to O.T. and MA-100, observed reactions to both tuberculins, but there were many more reactions to MA-100 than to O.T. The majority of these reactions reached their maximum size in 24 hours and were characterized by a soft, boggy oedema in contrast to the dark red, indurated reaction at 48 hours of the usual tuberculin reaction. These authors interpreted the increased number of reactions to MA-100 as evidence of sensitization induced by previous injection of this tuberculin. Steele and Willis (12) likewise believed that they had induced sensitization to both T.P.T. and O.T. by a series of three injections of each. However, they found a greater number of reactions to O.T. on subsequent tests. In contrast to these results Barnwell and Pollard (13) secured a greater number of reactions to T.P.T. than to O.T. both with original and repeated tests with larger dosage and felt that this phenomenon was not due to sensitization but rather to the detection of a greater number of persons with tuberculous allergy, and also that the larger number of reactions to T.P.T. was evidence of the greater sensitivity of this tuberculin. In support of this view they called attention to the fact that they were unable to sensitize 39 new-born infants by repeated injections of O.T. and T.P.T., and also that a number of young adults failed to react to from 5 to 24 repeated tests with both O.T. and T.P.T.

Our own interest in this problem was stimulated by the observation that there was an increased percentage of reactions in a group of children who were being tuberculin tested at yearly intervals. In 1932 O.T. alone was employed and in 1933 simultaneous tests were made with O.T. and MA-100 and a second test was performed with increased doses of each tuberculin in the negative and doubtful reactors. The histograms in chart 1 show the similarity of the response to O.T. in 1932 and 1933. In contrast to these results, we found in 1934 that there was a distinct increase in the number of reactions both to O.T. and MA-100.

This increase was due largely to a greater number of small reactions. The explanation of this greater percentage of reactions was not known, and, although it was realized that many of them were of questionable significance because of their small size, two possible explanations were considered: first, that they were due to recent tuberculous infection, and second, that they represented tuberculin-induced sensitization.

Seibert (14) and later Smithburn, Sabin and Geiger (15) demonstrated conclusively that nontuberculous experimental animals could be sen-

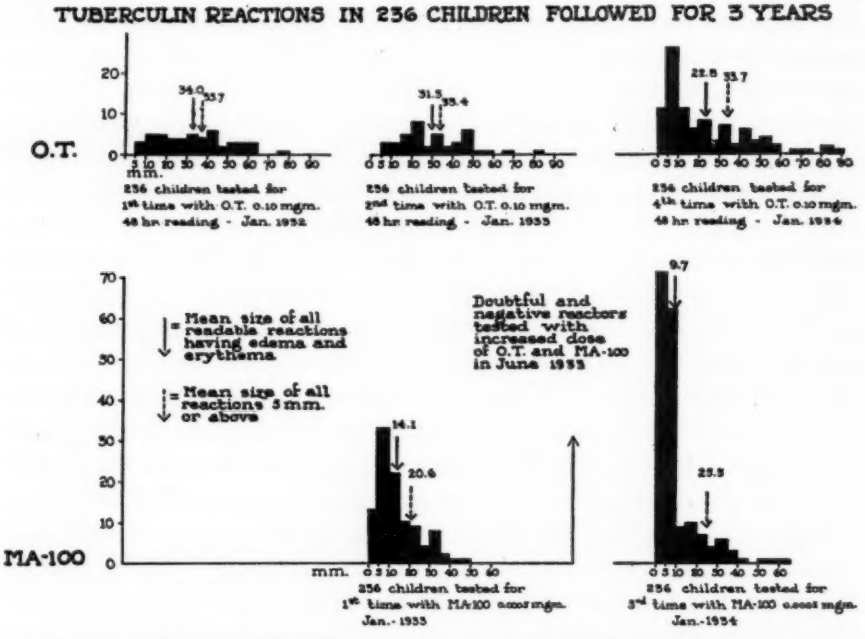

TUBERCULIN REACTIONS IN 256 CHILDREN FOLLOWED FOR 3 YEARS
O.T.
MA-100
mm.
34.0
33.7
31.5
33.4
22.8
33.7
256 children tested for 1st time with O.T. 0.10 mgm. 48 hr reading - Jan. 1932
256 children tested for 2nd time with O.T. 0.10 mgm. 48 hr reading - Jan. 1933
256 children tested for 4th time with O.T. 0.10 mgm. 48 hr reading - Jan. 1934
= Mean size of all readable reactions having edema and erythema
= Mean size of all reactions 5 mm. or above
Doubtful and negative reactors tested with increased dose of O.T. and MA-100 in June 1933
14.1
20.6
9.7
25.5
256 children tested for 1st time with MA-100 0.0005 mgm. Jan.-1933
256 children tested for 3rd time with MA-100 0.0005 mgm. Jan.-1934

CHART 1. Histograms illustrating the frequency and size of tuberculin reactions in a group of children at three annual injections. Note the increased number of small reactions to the test in January, 1934.

sitized readily to tuberculoprotein (T.P.T. and MA-100). In contrast Seibert (14) found that a preparation of O.T. (O.T.T.) had little or no sensitizing property. Later she (16) showed that the antigenic capacity of tuberculoproteins was related to their molecular size. Thus, T.P.T. and MA-100, which are of relatively large molecular size, are good antigens in contrast to the poor antigenicity of O.T. whose protein has a low molecular weight. By treating tuberculoprotein with weak alkali or by heating it, Seibert (17) was able to produce a tuberculin (P.P.D.)

of low molecular weight which retained its ability to detect tuberculous allergy and yet was not antigenic for animals. Seibert (18) found subsequently that adsorption of tuberculoprotein of low molecular weight to aluminium hydroxide or to charcoal restored its antigenic properties. This is of interest in that practically all of the workers who have reported sensitization to O.T. have used some additional substance (19) such as the serum of various animals, different vaccines and the like. There is suggested the possibility that a haptene phenomenon is concerned, according to the theory of Landsteiner (20). Reichle and Goldblatt (19) reported sensitization of guinea pigs with both O.T. and T.P.T. together with various adjuvant substances such as horse serum and eye fluid of normal guinea pigs, as well as sensitization of two animals with O.T. alone. They believed, however, that it was probable that an adjuvant substance is not necessary and that the essential element in the successful artificial sensitization to tuberculin is the tuberculin itself.

In view of these varied results it seemed advisable to attempt to answer the question: *Is tuberculin, in amounts ordinarily used for skin testing, capable of producing sensitization to itself in man and, if so, do different tuberculins vary in this respect?* A study was planned to test this question and it was decided to use O.T. for the first injections to eliminate the positive tuberculin reactors. At the suggestion of Esmond R. Long, the study was postponed until P.P.D. was available. It appeared justifiable to use this tuberculin for the "screening tests" in view of Seibert's (16, 17) evidence of its nonantigenicity.

## METHOD OF STUDY

We had planned originally to eliminate from a large group of children all those who had positive tuberculin reactions, and, in separate groups of the negative reactors, to make two injections of P.P.D., O.T. and MA-100, respectively, at intervals of 48 hours. Subsequently, tuberculin tests with P.P.D. were to be made in the three subgroups as well as in a fourth or control group at weekly intervals for two weeks and then at monthly intervals for two or three months. (See table 1.) The results were so irregular and inconsistent that it not only seemed advisable to make more tests in this group, but also to perform a similar series of tests in another group of children. Testing of this second group appeared to be particularly necessary, since all of the children of the first group received P.P.D. in eight or more tests. If, therefore, this tuberculin had an antigenic effect, all of the children would have been

affected by it. The second group (tables 5 & 6) was divided equally into two subgroups, the one receiving O.T. throughout, and the other P.P.D. This group was composed of infants and small children and, although the rates of reactions[3] were much lower than in group 1 (tables 1 & 3), the same inconsistencies were observed in the individual responses. Twenty-four hour readings were made only in the last test (test 14) of the first group and in the last two tests (tests 9 and 10) of the second group. In each instance the mean size of the reactions for the group was larger at 24 hours than at 48 hours. The question was raised whether this peak response at 24 hours might be evidence of a low degree of tuberculin allergy, possibly induced by the previous tuberculin injections. Two other groups (groups 3a and 3b) were selected, one for P.P.D and the other for O.T., and repeated tests were performed (tables 7, 8 & 9) in which readings were made in all tests at 24 and 48 hours.

Except in group 2 the sites of the injections were varied to avoid the possibility of local sensitization. In group 2 the flexor surfaces of the two forearms were alternately employed so that the same site was used for every other injection.

### *Detail of Groups*

*Group 1:* (Tables 1, 2, 3 & 4) A group of 613 children living in the Ohio Soldiers' and Sailors' Orphans' Home at Xenia, Ohio, who had not been tuberculin tested previously, were injected intracutaneously with 0.000,02 mgm. of P.P.D. Of these, 111 had reactions 5 mm. or larger in diameter and were not tested further. Forty-eight hours after this first test, the remaining 502 children were injected intracutaneously with 0.005 mgm. of P.P.D. and in 311 there were no reactions whatsoever at the end of 48 hours. These 311 children constituted the test group. They were divided into four groups of essentially equal size and of equal age distribution (4 to 18 years). One group was designated as a control group and was not tested in tests 3 and 4; the other three subgroups received respectively, at intervals of 48 hours, two injections of 0.1 cc. of 1:100 O.T., 0.005 mgm. of P.P.D. and 0.001 mgm. of MA-100 (tests 3 & 4, table 1). All four subgroups were injected with P.P.D. in tests 5 to 9 inclusive. The intervals between tests are shown in table 1. Test 9 was performed after the children had returned to the Home from their

[3] The term "rate of reaction" is used in the text and in the tables to indicate the numerical response of the group and not the speed of development of the skin reaction. For example, "0.220" is 220 positive reactions per 1,000 tested subjects, or, in other words, 22 per cent.

TABLE 1

*Summary of group 1—Repeated tests with various tuberculins*

| | | SECTION 1 | | | SECTION 2 | | | | | | SECTION 3 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 P.P.D. 0.000,02 mgm. | 2 P.P.D. 0.005 mgm. | 3 | 4 | 5 P.P.D. 0.005 mgm. | 6 P.P.D. 0.005 mgm. | 7 P.P.D. 0.005 mgm. | 8 P.P.D. 0.005 mgm. | 9 P.P.D. 0.005 mgm. | 10 | 11 | 12 | 13 | 14 P.P.D. 0.005 mgm. |
| Size† | Whole Group 613 | 12.1 | 16.3 | | | | | | | | | | | | |
| | P.P.D. Group* | | | P.P.D. 5.4 | P.P.D. 6.3 | 5.8 | 5.4 | 9.6 | 12.4 | 7.5 | P.P.D. 0.005 11.5 | P.P.D. 0.005 5.7 | P.P.D. 0.005 9.1 | P.P.D. 0.005 6.3 | 4.9 |
| | O.T. Group | | | O.T. 7.7 | O.T. 11.2 | 5.8 | 5.9 | 7.7 | 11.4 | 7.3 | | | | | 10.1 |
| | MA-100 Group | | | MA-100 4.5 | MA-100 6.1 | 7.2 | 6.4 | 10.3 | 14.2 | 8.4 | MA-100 4.7 | MA-100 5.7 | MA-100 6.1 | MA-100 9.9 | 9.3 |
| | Control Group | | | | | 8.2 | 5.9 | 8.9 | 14.1 | 8.9 | | | | | 8.6 |
| Rate‡ | Whole Group | 0.220 | 0.317 | | | | | | | | | | | | |
| | P.P.D. Group | | | 0.313 | 0.289 | 0.193 | 0.145 | 0.373 | 0.470 | 0.152 | 0.385 | 0.177 | 0.354 | 0.102 | 0.064 |
| | O.T. Group | | | 0.107 | 0.253 | 0.200 | 0.093 | 0.267 | 0.386 | 0.112 | | | | | 0.229 |
| | MA-100 Group | | | 0.096 | 0.151 | 0.260 | 0.096 | 0.342 | 0.493 | 0.214 | 0.043 | 0.129 | 0.319 | 0.209 | 0.179 |
| | Control Group | | | | | 0.286 | 0.043 | 0.232 | 0.406 | 0.212 | | | | | 0.212 |
| Days after preceding test | | 2 | 2 | 2 | 9 | 7 | 35 | 21 | 140 | 56 | 28 | 28 | 28 | 21 | |
| Days after test 1 | | 2 | 4 | 6 | 15 | 22 | 57 | 78 | 218 | 274 | 302 | 330 | 358 | 379 | |

* The four subgroups are composed of 311 children who had no reaction whatsoever at 48 hours in tests 1 and 2.

P.P.D. was employed in all children in tests 1 and 2, 5 to 9 inclusive, and in test 14.

The tuberculins which designate the groups were employed in tests 3 and 4 and in tests 10 to 13 inclusive.

The "probable error" for the calculations in this and subsequent tables has been determined. The data have been omitted from the tables for the sake of simplification. Copies of the complete tables including the calculations of the "P.E." may be had upon request from the authors.

† Indicates mean size in mm. of all measurable reactions having oedema and erythema at 48 hours.

‡ Indicates rates of positive reactions (see footnote 3 of text), that is, all reactions 5 mm. or greater in diameter having oedema and erythema.

summer vacations. Tests 10 to 14 inclusive were designed to measure the effects of monthly injections (P.P.D. and MA-100 groups) in contrast to a longer period without injections (O.T. and control groups) and also to test further the differences in response to P.P.D. and MA-100. During the two years since the first test was performed in this group, 163 new children were admitted to the institution. An attempt was made to determine if there was any difference in the response of this group (not previously tested with tuberculin) to 0.005 mgm. of P.P.D. from that of children in the group who had received 14 repeated tests. All of the children in the institution were tested with 0.000,02 mgm. of P.P.D. and those who failed to have positive reactions were retested 48 hours later with 0.005 mgm.[4] The rates of reactions of the children who had received 14 injections of tuberculin are compared in table 4 with the new group of children who had not been tuberculin tested previously.

TABLE 2

*Comparison of 24- and 48-hour reactions of test 14, group 1—all groups tested with 0.005 mgm. P.P.D.*

| | | P.P.D. GROUP | O.T. GROUP | MA-100 GROUP | CONTROL GROUP |
|---|---|---|---|---|---|
| Size | 24 hours | 11.3 | 13.5 | 13.7 | 12.6 |
| | 48 hours | 4.9 | 10.1 | 9.3 | 8.6 |
| Rate | 24 hours | 0.701 | 0.829 | 0.761 | 0.712 |
| | 48 hours | 0.064 | 0.229 | 0.179 | 0.212 |

Only those reactions having both oedema and erythema and which were 5 mm. or larger in diameter were considered to be positive and, therefore, to be included in "Rates of Reactions" in table 1. The "Sizes of Reaction" in table 1 are measurements of erythema since oedema was not separately measured until after test 6. However, no reaction without oedema is included in this table. Separate oedema and erythema measurements were made in tests 7 to 14 inclusive, and also in all tests in the other groups which are detailed in other tables. In all but tables 1, 2 and 3, all "Sizes of Reactions" and "Rates of Reactions" are based upon readings of oedema. The differences arising from calculations based on measurements of oedema in contrast to measurements of erythema will be considered later.

[4] None of the children who had had 14 injections of tuberculin had positive reactions to the test with 0.000,02 mgm. P.P.D.

TABLE 3

*Examples of response to repeated tests in individual children from group 1*

| SUBGROUP* | CASE NUMBER | MEASUREMENT OF ERYTHEMA, ALL REACTIONS HAD OEDEMA | | | | | | MEASUREMENT OF OEDEMA | | | | | | | | TOTAL NUMBER OF POSITIVE REACTIONS | ROENTGENOLOGICAL EVIDENCE OF TUBERCULOSIS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 | Test 6 | Test 7 | Test 8 | Test 9 | Test 10 | Test 11 | Test 12 | Test 13 | Test 14 | | |
| P.P.D. | 8 | | | 8.5 | | | 11.5 | | 11.0 | 5.0 | 11.5 | 5.5 | | 7.0 | 5.0 | 8 | + |
| | 31 | | | 5.0 | | | | 10.0 | 8.0 | | 11.0 | 5.0 | 12.0 | | 5.5 | 7 | 0 |
| | 41 | | | | | | | | | | 5.0 | | 6.0 | | | 2 | + |
| | 51 | | | | | | | | | | | | | | | 0 | + |
| | 81 | | | | | | | 13.0 | | | 11.0 | | | 13.0 | | 3 | 0 |
| MA-100 | 8 | | | | | | | 16.5 | 18.5 | | | | | 6.5 | 15.0 | 4 | + |
| | 31 | | | 5.0 | 20.0 | 16.5 | | 19.0 | 21.5 | 25.0 | | | 6.5 | | 25.0 | 8 | + |
| | 48 | | | | | | | | | | | | | | | 0 | + |
| | 50 | | | | | | | 11.5 | 17.0 | | | | | | | 2 | ? |
| | 70 | | | | 9.5 | 6.0 | | | 5.0 | | | | 5.0 | | | 4 | ? |
| O.T. | 9 | | | | | | | | | | Not tested | | | | 13.0 | 1 | + |
| | 14 | | | 8.5 | 17.0 | | | | 5.0 | | Not tested | | | | | 3 | + |
| | 30 | | | | 5.5 | 8.0 | | | 5.0 | 5.5 | Not tested | | | | | 4 | 0 |
| | 41 | | | | | | | | | | Not tested | | | | | 0 | + |
| | 70 | | | | | | | | | | Not tested | | | | | 0 | + |
| Control | 9 | | | Not tested | | 10.5 | | 5.0 | | | Not tested | | | | | 2 | 0 |
| | 13 | | | Not tested | | 18.0 | 66.0 | 43.5 | 43.5 | Not tested in subsequent tests | | | | | | 4 | + |
| | 24 | | | Not tested | | | | | 8.0 | 5.0 | Not tested | | | | | 2 | + |
| | 34 | | | Not tested | | | | 7.5 | 12.5 | | Not tested | | | | 19.0 | 3 | ? |
| | 69 | | | Not tested | | | | | | | Not tested | | | | | 0 | + |

* P.P.D. was employed in all children in tests 1 and 2, 5 to 9, inclusive, and in test 14.
The tuberculins which designate the subgroups were employed in tests 3, 4 and 10 to 13, inclusive.
Measurement = Mean diameter in mm.
Only reactions with a diameter of 5 mm. or more are recorded here.

TABLE 4

*Comparative rates of positive reactions to 0.005 mgm. P.P.D. of a group of children who had received repeated injections of tuberculin with those of a group who had not had repeated injections*

| GROUP | TEST 14 MARCH, 1936 | | TEST 16 FEBRUARY, 1937 | |
|---|---|---|---|---|
| | 24 hr. | 48 hr. | 24 hr. | 48 hr. |
| Previously tested* | 0.645† | 0.139† | 0.670 | 0.242 |
| Not previously tested** | | | 0.731 | 0.323 |

* Combined subgroups of group 1. Entirely negative to tests 1 and 2, varying rates of reactions in subsequent tests.

** Children in same institution who had not been tuberculin tested previously except for "screening" test with P.P.D. 1 and O.T. 1 forty-eight hours before. None of the children included here had positive reactions to the first test.

† These rates are based only on the data of the 231 children who were retested in February, 1937.

TABLE 5

*Summary of group 2—Percentage of reactions 5 mm. or greater in diameter at 48 hours*

| TEST NUMBER | SUBGROUP 3A P.P.D. (45 CASES) | | SUBGROUP 3B O.T. (47 CASES) | | INTERVAL BETWEEN TESTS | INTERVAL AFTER TEST 1 |
|---|---|---|---|---|---|---|
| | Number | Per cent | Number | Per cent | | |
| | | | | | *days* | *days* |
| 1 | 3 | 6.67 | 0 | 0 | 0 | 0 |
| 2 | 4 | 8.89 | 1 | 2.13 | 2 | 2 |
| 3 | 0 | 0 | 2 | 4.26 | 2 | 4 |
| 4 | 5 | 11.11 | 2 | 4.26 | 2 | 6 |
| 5 | 3 | 6.67 | 0 | 0 | 9 | 15 |
| 6 | 5 | 11.11 | 1 | 2.13 | 7 | 22 |
| 7 | 3 | 6.67 | 2 | 4.26 | 35 | 57 |
| 8 | 6 | 13.33 | 1 | 2.13 | 21 | 78 |
| 9 | 7 | 15.56 | 3 | 6.38 | 71 | 149 |
| 10 | 6 | 13.33 | 4 | 8.51 | 62 | 211 |
| Total number reactors in 10 tests | 16 | | 7 | | | |

Sizes and rates are based on measurements of oedema.

*Group 2 (a & b)*: (Tables 5 & 6) A group of 95 infants and children, residents of the St. Joseph's Infant Asylum, ranging in age from a few weeks to six years, was divided into two equal subgroups, each with an equal age distribution. One subgroup was tested throughout with P.P.D. (group 2a) the other with O.T. (group 2b). Subgroup 2a re-

ceived 0.000,02 mgm. of P.P.D. in test 1 and 0.005 mgm. in the remaining ones. Subgroup 2b received 0.1 cc. of 1:1000 O.T. in the first test and 0.1 cc. of 1:100 in subsequent tests. In order to see whether there were any differences in the response to repeated tests in children who had small and questionably positive reactions in tests 1 or 2 in contrast to those who had no reactions in these tests, all of the children, except one who had a definitely positive reaction, were included in the subsequent tests. In this respect this group was, therefore, treated differently from the

TABLE 6

*Examples of response to repeated tuberculin tests in individual children from group 2*

| TUBERCULIN | CASE NUMBER | TEST 1 | TEST 2 | TEST 3 | TEST 4 | TEST 5 | TEST 6 | TEST 7 | TEST 8 | TEST 9 | TEST 10 | TOTAL NUMBER OF POSITIVE REACTIONS | ROENTGENOLOGICAL EVIDENCE OF TUBERCULOSIS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P.P.D. | 8 | | | | 3.5 | | | 7.5 | 3.0 | 4.0 | 4.5 | 1 | 0 |
| | 43 | 3.0 | | 3.0 | | 3.0 | 4.5 | | | 3.0 | 3.0 | 0 | |
| | 50 | 5.5 | 4.0 | | 4.0 | 4.0 | | 3.5 | 3.0 | 4.0 | 3.5 | 1 | 0 |
| | 53 | 3.0 | 5.0 | | 10.0 | 14.0 | 20.0 | | 6.5 | 6.0 | 3.5 | 6 | ? |
| | 56 | 6.0 | 2.5 | 3.0 | 4.0 | 3.0 | 6.5 | 2.0 | 3.0 | 3.0 | 8.5 | 3 | 0 |
| O.T. | 6 | | | | | | 3.0 | | | | 4.0 | 0 | |
| | 19 | | | | | | | 4.0 | | 8.5 | 10.0 | 2 | 0 |
| | 32 | | | 11.0 | 12.0 | | 15.0 | | 9.5 | 8.5 | 5.5 | 6 | 0 |
| | 44 | | 3.5 | | 3.0 | 3.5 | 2.5 | | | 8.0 | 3.0 | 1 | |
| | 49 | 3.5 | | | 3.5 | | 4.0 | | 3.0 | 3.0 | 3.0 | 0 | |

Measurement = mean diameter in mm. of oedema.
All measurable reactions are recorded.

first. Ten injections were made, the first eight of which were at the same intervals as those of the first group.

*Group 3:* (Tables 7, 8 & 9) One group (subgroup 3a) of 51 children, residents of Glenview School, was tested entirely with P.P.D. and another group (subgroup 3b) of 75 children, residents of the Madisonville Children's Home, was tested with O.T. The children in these groups ranged in age from 4 to 18 years. The dosages employed were the same as in group 2, a small dose for the first test and a larger one for the later tests. It was planned to make four tests in each group at 48-hour intervals and subsequent ones at periods of four weeks. Those children who had

definitely positive reactions in tests 1 or 2 were eliminated from the subsequent tests, but, as in group 2, the children who had small, questionably positive reactions in tests 1 or 2 were included in the subsequent tests. Both 24- and 48-hour measurements of oedema and erythema were recorded. So many of the children in the P.P.D. group were

TABLE 7

*Summary of group 3a—repeated tests with P.P.D.*

| | | TEST 1 0.000,02 MGM. | TEST 2 0.005 MGM. | TEST 3 0.005 MGM. | TEST 4 0.005 MGM. |
|---|---|---|---|---|---|
| Size | 24 hr. | 3.2 | 7.4 | 7.2 | 8.9 |
| | 48 hr. | 3.2 | 5.3 | 6.3 | 6.2 |
| Rate | 24 hr. | 0 | 0.722 | 0.500 | 0.833 |
| | 48 hr. | 0 | 0.111 | 0.278 | 0.500 |
| Days after preceding test | | | 2 | 2 | 2 |
| Days after test 1 | | | 2 | 4 | 6 |

Sizes and rates are based on measurements of oedema.

TABLE 8

*Summary of group 3b—Repeated tests with O.T. Mean size in mm. of all measurable reactions having oedema and erythema. Rates of all positive reactions*

| | | TEST 1 1:1000 | TEST 2 1:100 | TEST 3 1:100 | TEST 4 1:100 | TEST 5 1:100 | TEST 6 1:100 | TEST 7 1:100 | TEST 8* 1:100 |
|---|---|---|---|---|---|---|---|---|---|
| Size** | 24 hr. | 4.5 | 6.8 | 5.9 | 9.3 | 8.6 | 12.0 | 8.6 | 6.4 |
| | 48 hr. | 3.5 | 4.9 | 5.5 | 6.4 | 6.3 | 9.4 | 6.4 | 7.5 |
| Rate** | 24 hr. | 0.052 | 0.552 | 0.293 | 0.758 | 0.758 | 0.758 | 0.741 | 0.500 |
| | 48 hr. | | 0.190 | 0.155 | 0.379 | 0.310 | 0.275 | 0.448 | 0.396 |
| Days after preceding test | | | 2 | 2 | 2 | 28 | 28 | 35 | 195 |
| Days after test 1 | | | 2 | 4 | 6 | 34 | 62 | 97 | 292 |

* Ten children less than in previous tests.

** Sizes and rates are based on measurement of oedema.

eliminated either because of positive reactions in tests 1 and 2 or because of sickness that this group was discontinued after the fourth test.

*Group 4:* (Chart 2) The question was raised whether the smaller reactions with a maximum size at 24 hours, which occurred as early as the second test in both subgroups of group 3, were nonspecific responses to a concentrated testing solution. For this reason it was decided to

test a number of infants with simultaneous injections with the first and second testing strengths of O.T. and P.P.D. respectively. Each infant,

TABLE 9

*Examples of response to repeated tuberculin tests in individual children from group 3a*

| CASE NUMBER | TIME OF READING | TEST 1 | TEST 2 | TEST 3 | TEST 4 | TEST 5 | TEST 6 | TEST 7 | TEST 8 | NUMBER OF POSITIVE REACTIONS | ROENTGENOLOGICAL EVIDENCE OF TUBERCULOSIS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 24 hr. | | | | 5.0 | 12.0 | 12.5 | 14.0 | 18.5 | 5 | 0 |
| | 48 hr. | | | | | 12.5 | 10.0 | 5.5 | 24.5 | 4 | |
| 5 | 24 hr. | | 8.0 | 9.0 | 10.0 | 12.0 | 12.5 | 11.5 | 6.5 | 7 | 0 |
| | 48 hr. | | | | | | 9.5 | 9.0 | 5.5 | 3 | |
| 14 | 24 hr. | 6.5 | 10.0 | 7.0 | 18.0 | 8.0 | 18.0 | 13.0 | 5.5 | 8 | ? |
| | 48 hr. | | 5.5 | | 12.0 | | | | 7.0 | 3 | |
| 21 | 24 hr. | | 8.5 | 7.5 | 9.0 | 6.5 | 14.5 | 9.0 | 6.0 | 7 | + |
| | 48 hr. | | 7.0 | | 5.0 | | | 6.0 | 6.5 | 4 | |
| 24 | 24 hr. | | | | 10.0 | | 12.0 | 5.0 | | 3 | 0 |
| | 48 hr. | | | | 11.0 | | 8.5 | | 5.0 | 3 | |
| 26 | 24 hr. | | 9.0 | 8.0 | 14.0 | 10.0 | 12.0 | 9.0 | 9.0 | 7 | ? |
| | 48 hr. | | | | 8.0 | 12.0 | 10.5 | | | 3 | |
| 42 | 24 hr. | | | | | | | | | 0 | 0 |
| | 48 hr. | | | | | | | | | 0 | |
| 44 | 24 hr. | 7.0 | 11.0 | 13.0 | 33.0 | 19.0 | 21.0 | 17.0 | 12.0 | 8 | + |
| | 48 hr. | | 6.5 | 8.0 | 8.5 | 8.5 | 18.5 | 9.5 | 10.0 | 7 | |
| 47 | 24 hr. | | 8.5 | | 19.0 | 13.5 | 15.5 | 10.5 | | 5 | 0 |
| | 48 hr. | | | 10.0 | 21.0 | 12.0 | 14.0 | 15.0 | 13.0 | 6 | |
| 62 | 24 hr. | | 6.0 | 6.0 | 15.0 | 6.5 | 10.0 | 7.5 | | 6 | 0 |
| | 48 hr. | | | | 10.0 | | | 6.0 | | 2 | |

Measurement = Mean diameter in mm. of oedema.
Only reactions with a diameter of 5 mm. or more are recorded here.

therefore, received four simultaneous tuberculin injections. The infants ranged in age from 18 days to 14 months and were residents at Maple Knoll, a foundling institution.

*Roentgenographic studies:* Roentgenograms of the chests were made of approximately half (chosen alphabetically) of the children in group 1 (Xenia), in all of group 3 (Glenview and Madisonville), of six children of group 2 who had positive reactions at one time or another, and of the five infants in group 4 (Maple Knoll) who had the largest reactions.

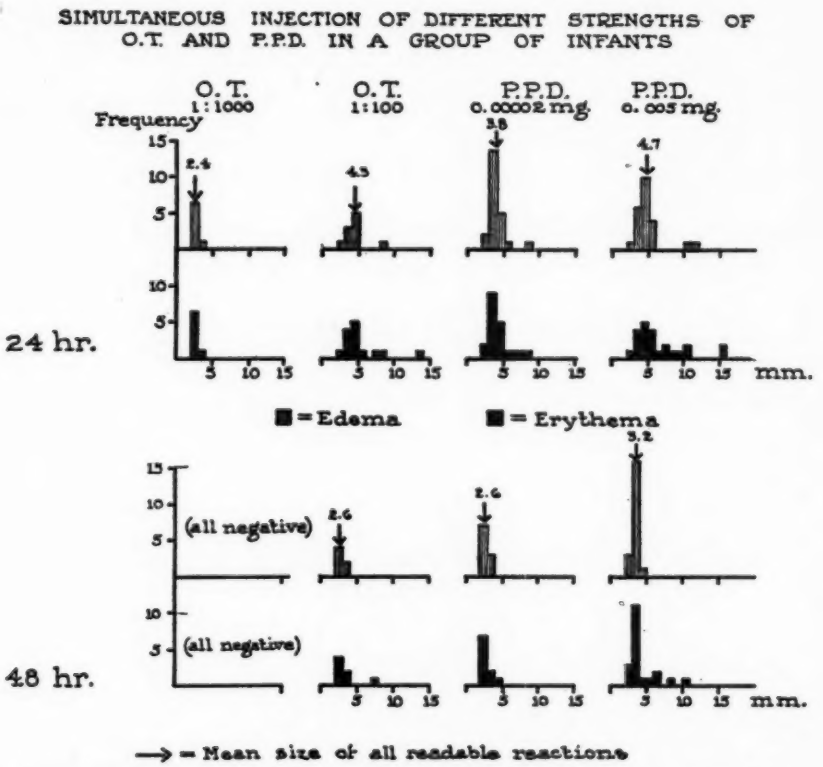



CHART 2. Simultaneous injections of different strengths of O. T. and P. P. D. in a group of 24 infants who had not been tested previously with tuberculin. The infants ranged in age from 18 days to slightly over one year.

## DISCUSSION OF DATA

*What constitutes a positive tuberculin reaction?* In view of the great number of small reactions it is desirable to discuss briefly the criteria acceptable as constituting a positive tuberculin reaction. It is generally stated that a positive cutaneous reaction to tuberculin is manifested by oedema and erythema at the end of 48 hours (21) and that the area of oedema should be more than 5 mm. in diameter (22). If there is no

oedema the reaction is not considered positive (21, 22). Judged by these criteria, we observed a considerable number of nonspecific reactions in all groups. In some instances there was erythema without oedema, in others a positive reaction at 24 hours with a subpositive reaction or with complete fading at 48 hours and in a considerable number of instances subpositive reactions at both 24 and 48 hours. Some children had subpositive reactions in all tests but more commonly there was an intermingling of positive and subpositive reactions. It is also to be noted that there was no correlation of the roentgenological findings with the different types of response to tuberculin. Evidences of intrathoracic tuberculosis were observed in children who had positive tuberculin reactions in tests 1 or 2, in those who had positive reactions only in one or more tests subsequent to the first two tests, and in those who had never more than a subpositive reaction.

*Erythema versus oedema measurements:* In some instances in which there was only erythema 48 hours after the injection there had been indurations at 24 hours. In others there was erythema without induration at 24 hours which at times persisted for 48 hours and in others had disappeared at this time. Although in some instances there was roentgenographic evidence of tuberculosis in children who had reactions consisting only of erythema, no reactions without oedema were considered to be positive. However, since the calculations of the first group were based on readings of erythema, it seemed advisable to see what differences, if any, existed between rates of positive reactions (5 mm. or greater in diameter), based separately on measurements of erythema and of oedema in reactions having both of these characteristics. The results from the Madisonville group (group 3a) were analyzed from this standpoint. The mean sizes of all reactions in the first seven tests of this series were 10.03 mm. for erythema and 7.96 mm. for oedema respectively, at 24 hours; and 7.99 mm and 6.06 mm. respectively, at 48 hours. Although these differences between the measurements of erythema and oedema are significant in each instance, the variations between the mean sizes in each test (1 to 7 inclusive) would not make a difference between positive and negative reactions for the entire group. However, if the measurements of erythema were accepted as the criterion for a positive reaction instead of the measurements of oedema, it will be noted in table 10 that there would have been a greater number of positive reactions both at 24 and 48 hours. Thus, the rates recorded for the Xenia group (group 1) were higher than if they had been recorded on the basis

of measurements of oedema, although the pattern of response for the group was not altered (table 1). Measurements of oedema were recorded for the Xenia group in tests 7 to 14 inclusive, and it was observed that the rate in this group (P.P.D.) was distinctly lower than in the Madisonville group (O.T.). This may represent different degrees of tuberculous infection in the two groups.

TABLE 10

*Comparison of measurements of oedema and erythema at 24 and 48 hours from group 3a*

| TEST NUMBER | | MEAN SIZE IN MM. | | NUMBER POSITIVE REACTORS | |
|---|---|---|---|---|---|
| | | Erythema | Oedema | Erythema | Oedema |
| 1 | 24 hr. | 4.5 | 4.5 | 3 | 3 |
| | 48 hr. | 3.5 | 3.5 | | |
| 2 | 24 hr. | 8.7 | 6.8 | 32 | 32 |
| | 48 hr. | 7.3 | 4.9 | 16 | 11 |
| 3 | 24 hr. | 8.9 | 5.9 | 20 | 17 |
| | 48 hr. | 6.3 | 5.5 | 9 | 9 |
| 4 | 24 hr. | 11.3 | 9.3 | 46 | 44 |
| | 48 hr. | 10.0 | 6.4 | 26 | 22 |
| 5 | 24 hr. | 12.7 | 8.6 | 50 | 44 |
| | 48 hr. | 8.5 | 6.3 | 20 | 18 |
| 6 | 24 hr. | 13.5 | 12.0 | 44 | 44 |
| | 48 hr. | 12.1 | 9.4 | 18 | 16 |
| 7 | 24 hr. | 10.6 | 8.6 | 45 | 43 |
| | 48 hr. | 8.2 | 6.4 | 27 | 26 |
| Average.... | 24 hr. | 10.03 | 7.96 | 34.29 | 32.43 |
| | 48 hr. | 7.99 | 6.06 | 19.33 | 17.0 |

*Twenty-four versus 48-hour readings:* It seems to be generally accepted that the skin reaction to a tuberculin injection reaches its peak sometime after 24 hours and that 48 hours is the most satisfactory time for reading the test. In our experience this was true for strongly positive reactions but not for the smaller ones. It will be seen in tables 7 and 8 that the size of the reaction at 24 hours was larger in all tests except test 8, table 8. This is shown for the individual child in table 9. Statistical analysis of the reactions at 24 and 48 hours in table 9 shows conclusively that the

size and the number of reactions were significantly greater at 24 hours in tests 2 to 7 inclusive than at 48 hours. While it is possible that a 24-hour peak response with partial or complete fading at 48 hours is evidence of a nonspecific reaction, this may not be invariably true in view of roentgenological evidence of tuberculous lesions associated with such reactions. This will be illustrated in a subsequent publication (23). In some instances we observed the type of maximum 24-hour response as described by Aronson and Nicholas (9), namely, that the color was a lighter red or pink and the area of induration was "boggy" or less tense than usual. Since this type of skin reaction was observed as early as the second injection and only 48 hours after the first injection, one could scarcely attribute it to tuberculin-induced sensitivity. It appeared more probable that the 24-hour maximum response was due, at least in some instances, to a low degree of allergy. That it might result, however, from artificially induced tuberculoprotein sensitivity does not seem improbable. In fact Smithburn, Sabin and Geiger (15) state that in guinea pigs which were sensitized to MA-100 tubercle bacillus protein some of the reactions were at their maximum size at 24 hours.

*Technical factors:* In view of the possibility that the smaller 24-hour peak reactions which occurred as early as the second test (tables 8 and 9) were nonspecific responses to a concentrated testing solution it was decided to test a number of infants with simultaneous injections of the first and second testing strengths of O.T. and P.P.D. respectively. Thus, each infant received four simultaneous tuberculin injections. The infants ranged in age from 18 days to 14 months. The results of the skin tests are shown in the histograms of chart 2. The reactions at 24 hours were invariably larger than those at 48 hours. It was observed that there were distinct differences for the four testing solutions. In order of their ability to elicit a reaction they were as follows: 0.005 mgm. P.P.D., 0.000,02 mgm. P.P.D., 1:100 O.T. and 1:1000 O.T. In regard to size of reactions the larger dose of P.P.D. was distinctly more potent, 1:100 O.T. and 0.000,02 mgm. P.P.D. were essentially equal, and 1:1000 O.T. was distinctly weak. Roentgenograms were taken of the chests of the five children with the largest skin reactions (all were less than 5 mm. of oedema). No evidence of pulmonary involvement was detected. Another initial test with 0.005 mgm. of P.P.D. was performed in a group of infants in another foundling institution with essentially similar results. In view of these observations it seems possible that reactions with oedema up to 5 mm. in diameter and with slightly larger erythema may

be due to nonspecific factors. These observations, however, do not invalidate the possibility that reactions of this size or larger, whose measurements are greater at 24 hours than at 48 hours, are evidence of a specific allergy to tubercle bacillus protein.

The possibility that errors in technique might account for some of the inconsistencies observed to repeated tests in individual children was considered. For this reason simultaneous injections of 0.005 mgm. P.P.D. were made in the right and left forearms of 26 children. There were, in general, no differences in the size of reactions for the group. The measurements in mm. of oedema were as follows: $8.6 \pm 0.68$ on the right arm and $8.8 \pm 0.61$ on the left arm at 24 hours, and $7.2 \pm 0.62$ on the right arm and $7.2 \pm 0.68$ on the left arm at 48 hours. The measurements for erythema were correspondingly similar. However, in three children the reactions on one arm would have been considered negative and on the other arm positive. The measurements for the two arms were as follows: 5 mm. oedema (right), 5 mm. erythema with no oedema (left); 3.5 mm. oedema (right), 5.5 mm. oedema (left); and 5 mm. oedema (right), 4.5 mm. oedema (left). These results also illustrate the fallacy of accepting too rigidly a minimal standard for positive and negative reactions.

While we do not feel that exact criteria for the separation of specific from nonspecific reactions can be stated categorically on the basis of present evidence, it would appear wiser to accept as a minimum basis an area of induration or oedema of 5 mm. in diameter. Although the occurrences of reactions of 3 to 5 mm. in diameter and occasionally slightly larger in three different groups of infants suggest the possibility of nonspecific irritative reactions, there is a strong possibility that in some of these instances such small reactions may be specific responses of a very low state of tuberculin allergy.

*The question of induced sensitization:* In general the pattern of response to repeated injections of tuberculin was similar in all groups. A significant number of children, who had no reaction whatsoever or who had small, subpositive or questionably positive reactions in either test 1 or 2, had reactions 5 mm. or larger in diameter in one or more of the subsequent tests but *there was a distinct lack of consistency in the individual response* (tables 1, 3, 5, 6, 7, 8 & 9). Examples of the individual reactions are shown in tables 3, 6 and 9. In table 6 (group 2) all measurable reactions are shown and it will be noted that in a considerable number of instances there were reactions less than 5 mm. in diameter. Similarly

a large number of small reactions was observed in groups 1 and 3, although only reactions with a diameter of 5 mm. or more are listed in tables 3 and 9.

*Group 1:* (Tables 1, 2, 3 & 4) In the hope of securing greater simplicity for the reader, the data for group 1, which are detailed in table 1, were divided into three sections. While we realize that such a division was arbitrary, it seemed justified for the purpose of illustrating more clearly the following factors: (*1*) the number of positive reactions which occurred as early as tests 3 and 4; (*2*) the similarity of the response of the control group to the other three subgroups in test 5, as well as in tests 6 to 9 inclusive; and (*3*) the similarity of response of all subgroups when the tests were performed with the same tuberculin (tests 5 to 9 inclusive, and test 14) and the dissimilarity when different tuberculins were employed. (See tables 1 & 2.)

It will be noted that a considerable number of reactions occurred in test 3. This seemed noteworthy since all of the children studied in this and subsequent tests had had no reactions whatsoever in the first two tests; and since this test was performed four days after the first one, there was scarcely a sufficient time to account for the development of sensitization from the first injection. The reason for the higher rate for P.P.D. in this group is not apparent, although the low rate to MA-100 may be due to the smaller testing dose. This low rate of reactions to MA-100 is continued in test 4 whereas the rates of reactions to P.P.D. and O.T. are essentially the same. Tests 5 to 9, in which all four groups received P.P.D., are interesting in that all four groups behaved in a similar manner. It will be noted that, while there is no significant difference in the rate of reactions in test 5 as compared with test 4, in test 6 there is a marked drop followed by a sharp increase in tests 7 and 8 and a decrease again in test 9. We have not been able to find a satisfactory explanation of these variations. If they were mirrored in the individual responses, one might speculate on such factors as desensitization during tests 4 and 5 because of their close proximity or a sensitizing effect operating during the longer periods between tests 6 and 7 and between tests 7 and 8. The smaller rate of reactions in test 9 might then be due to a decrease of this artificially induced sensitivity in the 140 days elapsing between tests 8 and 9. The marked inconsistency of the reactions of individual children, however, makes it difficult to explain these observations on a group basis. Examples of reactions of individual children are shown in table 3 for this group and in tables 6 and 9 for groups 2 and

3a respectively. A point against the factor of desensitization in tests 3 to 5 inclusive is the behavior of the control group, which, although these children received no injections during tests 3 and 4, responded in exactly the same manner to tests 5 to 9 inclusive as the other subgroups. There were the same individual inconsistencies although the group reactions were similar to those of the other three groups. There were no epidemics of infections which might have nonspecifically affected the skin response during this period, nor were there sufficient climatic variations to explain such differences in the short time elapsing between tests 6 and 7 and between tests 11 and 12. There appears to be no plausible explanation whatsoever for the inconsistencies observed in the P.P.D. group in tests 10 to 13 inclusive. The low response to MA-100 in tests 10 and 11 may again be due to the low dosage (0.001 mgm.). Should one then interpret the increased rate in test 12 as the result of sensitization in tests 10 and 11 by a protein of high molecular weight? This appears highly questionable since a lower rate was obtained in test 13 when a larger dose of MA-100 (0.005 mgm.) was employed. Test 14, in which 0.005 mgm. of P.P.D. was injected in the children of all four groups, was designed to test the difference, if any, between the effect of repeated injections of tuberculin and a lapse of time (161 days) without injection of tuberculin. It appears that under the conditions of this experiment there are no differences. All but the P.P.D. group behaved in a similar manner. In relation to this, the results of the 24-hour reading of this test should be examined (see table 2). The 24-hour response in regard to size and percentage of reactions is the same for all groups. The P.P.D. group appeared to differ only in the rapidity of decrease in size between the 24- and 48-hour readings.

In table 4 are shown the 24- and 48-hour rates of reactions of those children who had had repeated injections of tuberculin in the four subgroups just described and also those of the new children in this institution who had not had repeated tuberculin tests. It will be noted that the character of the responses of the children who had received repeated injections was the same in test 16 as it had been in test 14 (one year earlier), and that there was no significant difference in the response of this group after two years of repeated tuberculin injections from that of the children who had not had repeated injections. (See discussion of 24 *versus* 48 hour size of reactions.) These results seem to us to be strong evidence against the argument of tuberculin-induced sensitization by the amounts of tuberculin employed in this series.

*Group 2:* (Tables 5 & 6) This group was composed of infants and young children. Since there was an insufficient number of positive reactions to give a stable rate, the results are stated in percentages and were examined by Fisher's method of the *Analysis of Variance.* The variation between the different tuberculins was so much larger than the variation from one test to another that the observed differences could not be attributed to a sensitizing effect of either tuberculin. There was a higher percentage of positive reactions in test 10 than in test 2 (the first test with the larger testing dose), but in actual number of reactions this represents a difference of only two in the P.P.D. group and of three in the O.T. group. Furthermore, it would appear significant that, although there were never more than seven positive reactions in any test in the P.P.D. group and more than four in any test in the O.T. group, there were 16 different children who had positive reactions in one or more tests in the P.P.D. group and seven in the O.T. group. The response of the children in group 2 to repeated injections of tuberculin does not appear to be due to tuberculin-induced sensitization. There were, however, variations in the responses to P.P.D. and to O.T. It is not clear whether these were due to differences between the two tuberculins or to a difference in the number of children with tuberculous infection in the two subgroups.

*Group 3:* (Tables 7, 8 & 9) In each of the tests after the first, the 24-hour reactions were larger and more numerous than the 48-hour ones (tables 7, 8 & 9). In contrast to this, those children who had strongly positive reactions in tests 1 and 2 had larger reactons at 48 hours. Roentgenograms of the chests were made of all the children. Correlation between the tuberculin reactions and the roentgenographic findings was, of course, impossible (23). However, it is significant that nine of the eighteen children in subgroup 3a (P.P.D.) had roentgenographic evidence of tuberculosis, in five the findings were questionable, and in four negative. An interesting example of a primary tuberculous complex with an extensive tracheobronchial lymph node involvement is shown in the following article ((23) figure 4, case 1C). The skin reaction to tuberculin in this boy was not of sufficient size to be considered positive until the fourth test. In this instance it would seem improbable that the reaction of the fourth test was due to sensitization induced by the first tuberculin injection.

Sizes and rates of reactions for the 24- and 48-hour readings of subgroup 3b (O.T.) are shown in table 8, and the individual variations as well as

the roentgenological readings in table 9. Since test 7 was the last of the series in which there was a relatively short interval between tests, it seemed of interest to compare the results of this test with those of the second, that is, the first test with the larger dose of tuberculin. Sizes and rates of reactions were both greater at 24 and 48 hours in test 7 than in test 2. Statistical analysis of these results revealed that both the 24- and 48-hour reactions of test 7 were significantly greater at the end of the 48 hours. The number of reactions, however, was not significantly greater at 24 hours. The explanation of these "significant differences" is not clear. Examination of the reactions of the individual children (table 9) did not reveal sufficient evidence of progressive increase in the reactions to support the theory of induced sensitization. For example, in cases 44 and 47, in each of which there is a fair continuity of positive reactions after tests 1 or 2, the sizes of the reactions were not appreciably different in tests 3, 7 and 8. It is true that both the number and the size of reactions were greater in test 3 than in test 2, but in subsequent tests there was no significant variation. To us it seemed more probable that these children had a low degree of tuberculin allergy from a pre-existing tuberculous infection rather than a tuberculin-induced sensitization. The inconsistent results represented by cases 14, 21, 24 and 26 defy an adequate explanation, but it is possible that they too represented an extremely low grade allergy which was readily depressed by more or less trivial factors. The results in case 2 were suggestive of sensitization by the previous injections, but this type of response was a distinct exception and might well be due to a recently acquired tuberculous infection. In those instances where there were only one or two reactions during the entire series of injections, the question was naturally raised whether these might be nonspecific responses. This could not be definitely answered. On the other hand, roentgenological evidence of tuberculous infection associated with tuberculin reactions of less than 5 mm. in diameter suggests the possibility that in some instances the reactions may be specific. It is not safe, however, to consider them as such since intracutaneous injections of physiological salt solution may cause reactions of 2 to 4 mm. in diameter at 24 hours and 2 to 3 mm. at 48 hours and tuberculin somewhat larger reactions in new-born infants.

In contrast to the high rate of tuberculin reactions in group 3b the roentgenological findings suggestive of tuberculosis were relatively few. If the high rate of tuberculin reactions in the later tests actually indicates tuberculous infection, it is possible that the small number of positive

roentgenological findings may be due to an early stage of the infection before calcification has occurred.

*Group 4:* In order to ascertain whether the infants in group 4 who had received four simultaneous injections of tuberculin had been sensitized they were retested 35 days later with 0.005 mgm. of P.P.D. The response was not different from that of the first test with this dosage of P.P.D.

*Analysis of results by age groups:* (Table 11) In an attempt to secure further information which might help to formulate a more definite opinion, the data of the various groups were analyzed from the standpoint of age. If there were a greater number of reactions in the older age group, in which presumably there were more opportunities for tuberculous infection, this would be one more argument against the

TABLE 11

*Analysis of repeated tuberculin tests by age groups*

| AGE IN YEARS | AVERAGE NUMBER OF POSITIVE REACTIONS PER REACTOR PER TEST | | |
|---|---|---|---|
| | Group 2 | Group 3a | Group 1 |
| 0–1 | .150 | | |
| 1–4 | .153 | .381 | |
| 5–9 | .275 | .325 | .178 |
| 10 and over | | .457 | .240 |

possibility of artificially induced sensitization. Since there may have been different amounts of tuberculous infection in the various institutions, the data from each were analyzed separately. There was a greater number of reactions per child per test in the group over 10 years of age and a distinctly smaller number among the infants.

*Studies in guinea pigs:* In a further study of this problem four groups of guinea pigs (3 in each group) were given 10 intracutaneous injections of 0.1 cc. of 1:100 O.T., of 0.1 cc. of 1:10 O.T., 0.005 mgm. of P.P.D. and 0.01 mgm. of MA-100, respectively, at intervals of 48 hours and skin tests were performed at intervals of 2, 3 and 37 weeks respectively. There was no evidence of cutaneous sensitization with the amounts of tuberculin used.

## SUMMARY

An attempt has been made to determine whether sensitization to tuberculin may be induced in man by amounts ordinarily used in skin

testing. Repeated tuberculin tests have been performed in several different groups of children who either had no reaction or not more than a small questionably positive one in either of the first two tuberculin tests. In some instances the evidence is such that induced sensitization might be suspected. The general pattern of the response to repeated injections, however, cannot be explained on this basis. While we cannot state definitely that the response to subsequent tuberculin injections has not been affected in some degree by the preceding ones, it would appear that other factors are concerned to a greater extent. That sensitization has been induced to tuberculin does not appear probable because (*1*) of the fact that the third injection was performed 96 hours after test 1, an interval presumably too short to permit induction of sensitization, (*2*) of the marked individual inconsistencies in the various series of tests, (*3*) of the failure to develop increasing rates of response or to secure increasingly larger reactions in the individual child, (*4*) of the roentgenological evidence of previous tuberculous infection in children who, although they did not react to the first two tests, did have reactions larger than 5 mm. of oedema in one or more of the subsequent tests, and (*5*) of the similarity of the 24- and 48-hour responses to 0.005 mgm. of P.P.D. of children who had had repeated injections over a period of two years with that of a group in the same institution who had no reactions to a test 48 hours previously with 0.000,02 mgm. of P.P.D. but who had not had repeated injections.

Speculation regarding the significance of the pattern of response observed has not developed an entirely adequate explanation. The most probable theory would appear to be that those children, who had positive reactions sometime subsequent to the two screening tests, had a low state of allergy from previous tuberculous infection. Such a theory, of course, allows for the possibility that some of the small reactions may be nonspecific ones. However, we know of no way of distinguishing the small nonspecific reactions from the specific ones of a similarly small size. Furthermore, while we accept, as a working basis, a minimal size limit of 5 mm. of oedema at 48 hours for positive tuberculin reactions, we are inclined to doubt that all 24-hour peak reactions with subpositive size at 48 hours are nonspecific. It would seem more probable that in some instances they represent a low state of tuberculin allergy. If the hypothesis just stated were true, how then would one account for such individual inconsistent responses as a variable number of positive, subpositive and negative reactions to different tests in the same child?

The only explanation that has seemed at all reasonable is that very low states of tuberculin allergy may be depressed by trivial factors, just as we have shown that stronger allergy may be depressed by acute illness (1). This is, of course, highly hypothetical.

Within the limits of the amounts of tuberculin injected in the various tests of this study, there appears to be no evidence that tuberculin sensitization is induced by tuberculin injection in man. This does not imply that sensitization to tuberculin or tuberculoprotein is impossible, but does indicate that such sensitization will probably not occur from the ordinary use of tuberculin for skin testing purposes.

## REFERENCES

(1) MITCHELL, A. G., NELSON, W. E., AND LEBLANC, T. J.: Studies in immunity; effect of acute diseases on reaction of skin to tuberculin, Amer. J. Dis. Child., 1935, *49*, 695.

(2) HAPP, W. M., AND CASPARIS, H. R.: Value of intracutaneous tuberculin test in extensive tuberculosis, Ibid., 1922, *23*, 527.

(3) JOHNSTON, J. A., HOWARD, P. J., AND MARONEY, J.: Quantitative study of tuberculin reaction in childhood tuberculosis, Amer. Rev. Tuberc., 1934, *29*, 652.

(4) STEWART, C. A., AND DYSON, R.: Sensitivity to tuberculin at different age periods, Amer. J. Dis. Child., 1936, *52*, 552.

(5) BALDWIN, E. R.: Studies in immunity to tuberculosis. 1 (a) Hypersusceptibility or anaphylaxis, Jour. Med. Research, 1910, *22*, 189.

(6) KRAUSE, A. K.: Studies in immunity to tuberculosis; hypersensitiveness to tuberculoprotein and its relation to some tuberculosis problems, Ibid., 1911, *24*, 361.

(7) LEWIS, P. A.: Relation of hypersusceptibility to immunity, Arch. Int. Med., 1909, *4*, 528.

(8) HAMEL, J.: Beitr. z. Klin. d. Tuberk., 1928, *68*, 345.

(9) ARONSON, J. D., AND NICHOLAS, R. V.: Comparative value of tuberculoprotein (MA-100) and Old Tuberculin, with special reference to sensitization, Jour. Immunol., 1933, *25*, 483.

(10) SEIBERT, F. B., AND MUNDAY, B.: Chemical composition of active principle of tuberculin; precipitated purified tuberculin protein suitable for preparation of standard tuberculin, Amer. Rev. Tuberc., 1932, *25*, 724.

(11) MASUCCI, P., AND MCALPINE, K. L.: Biochemical studies of bacterial derivatives. X. Preparation of human tubercle bacillus proteins MA-100, Proc. Soc. Exper. Biol. & Med., 1929–30, *27*, 661.

(12) STEELE, A. H., AND WILLIS, H. S.: Study of the increase of sensitiveness in normal children produced by repeated injections of tuberculin, Natl. Tuberc. Assn. Tr., 1934, p. 120.

(13) BARNWELL, J. B., AND POLLARD, H. M.: Comparison of Old Tuberculin with tuberculin protein T.P.T., Amer. Rev. Tuberc., 1934, *30*, 482.

(14) SEIBERT, F. B.: Chemical composition of active principle of tuberculin; local cutaneous sensitization (Arthus' phenomenon) produced in normal rabbits and guinea pigs by protein of tuberculin, Jour. Infect. Dis., 1932, *51*, 383.

(15) SMITHBURN, K. C., SABIN, F. R., AND GEIGER, J. T.: Effects of tuberculoprotein (MA-100) on course of experimental tuberculosis in rabbits and guinea pigs, Amer. Rev. Tuberc., 1934, *29*, 562.

(16) SEIBERT, F. B.: Relationship between the sensitizing properties of tuberculo-protein and its molecular weight, Natl. Tuberc. Assn. Tr., 1933, pp. 1–7.
(17) SEIBERT, F. B.: Isolation and properties of purified protein derivative of tuberculin, Amer. Rev. Tuberc., 1934, *30*, 713.
(18) SEIBERT, F. B.: Chemical composition of active principle of tuberculin; differences in antigenic properties of various tuberculin fractions; adsorption to aluminium hydroxide and charcoal, Jour. Immunol., 1935, *28*, 425.
(19) REICHLE, H. S., AND GOLDBLATT, H.: Sensitization of guinea pigs and production of allergy and anaphylaxis to tuberculoprotein, Amer. Rev. Tuberc., 1933, *27*, 291.
(20) LANDSTEINER, K.: Ueber heterogenetisches Antigen und Hapten, XV. Mitteilung über Antigene, Biochem. Ztschr., 1921, *119*, 294.
(21) Diagnostic Standards, ed. 10, Natl. Tuberc. Assn., New York City, 1935.
(22) ARONSON, J. D.: Purified protein derivative, with special reference to technique of tuberculin injections and grading of reactions, Amer. Rev. Tuberc., 1934, *30*, 727.
(23) NELSON, W. E., MITCHELL, A. G., AND BROWN, E. W.: The intracutaneous tuberculin reaction associated with calcified intrathoracic lesions, Ibid., 1938, *37*, 311.

# THE INTRACUTANEOUS TUBERCULIN REACTION ASSOCIATED WITH CALCIFIED INTRATHORACIC LESIONS[1,2]

WALDO E. NELSON, A. GRAEME MITCHELL AND ESTELLE W. BROWN

In the course of a study to determine whether the intracutaneous injection of tuberculin might have an antigenic effect in man (1), roentgenograms of the chests were taken of many of the children in the various groups. This was particularly necessary, since a number of the children who failed to react to either of the first two tuberculin tests had positive reactions on subsequent testing. We have stated our reasons for not believing that these later reactions were the result of sensitization induced by tuberculin. One of the factors responsible for this conclusion was the roentgenological evidence of tuberculous infection in some of the children who either had no reaction to tuberculin in repeated tests or who had reactions only in one or more tests after the first two "screening" tests. We were not surprised at the absence of roentgenological evidence of pulmonary tuberculosis in some of the children who had definite cutaneous reactions to tuberculin, but we were impressed by the fairly large number who, having roentgenological evidence of tuberculosis, either failed to react to tuberculin entirely or had positive reactions only in certain of the tests and no reactions or subpositive ones in others.

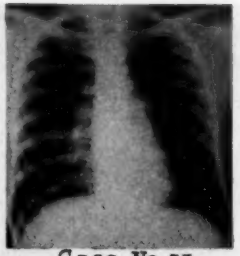
TABLE 1

*Comparison of tuberculin reactions with roentgenological evidence of calcification in the chest*

| | ROENTGENOLOGICAL EVIDENCE OF CALCIFICATION | | | | | |
|---|---|---|---|---|---|---|
| | Positive | | Questionable | | Negative | |
| | Number of cases | Per cent | Number of cases | Per cent | Number of cases | Per cent |
| Tuberculin positive to tests 1 or 2..... | 85 | 42.9 | 43 | 21.7 | 70 | 35.4 |
| Tuberculin positive to some later tests.. | 48 | 41.8 | 22 | 19.1 | 45 | 39.1 |
| Tuberculin negative..... | 27 | 43.5 | 5 | 8.1 | 30 | 48.4 |

[1] From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.

[2] Presented in abstract before the American Pediatric Society, Hot Springs, Virginia, April 30, 1937.



Case No. 55

| Test No. | 1 PPD | 2 PPD | 3 MA. 100 | 4 MA. 100 | 5 PPD | 6 PPD | 7 PPD | 8 PPD | 9 PPD | 10 MA. 100 | 11 MA. 100 | 12 MA. 100 | 13 MA. 100 | 14 PPD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 hr. | | | | | | | | | | | | | | N |
| 48 hr. | N | N | N | N | N | • | N | N | ⊙ | N | N | ● ↑ | N | N |

Case No. 299

| Test No. | 1 PPD | 2 PPD |
|---|---|---|
| 48 hr. | N | ▨ ↑ |

↑ Indicates 5mm. or above
N = No reaction
○ = Erythema
● = Edema
◉ = Edema and Erythema not measured separately
Scale • = 5mm.

Fig. 1

Case No. 41

| Test No. | 1 PPD | 2 PPD | 3 OT | 4 OT | 5 PPD | 6 PPD | 7 PPD | 8 PPD | 9 PPD | 10 PPD |
|---|---|---|---|---|---|---|---|---|---|---|
| 24 hr. | | | | | | | | | | N |
| 48 hr. | N | N | N | N | • | N | N | N | • | N |

Case No. 68

| Test No. | 1 PPD | 2 PPD | 3 OT | 4 OT | 5 PPD | 6 PPD | 7 PPD | 8 PPD | 9 PPD | 10 PPD |
|---|---|---|---|---|---|---|---|---|---|---|
| 24 hr. | | | | | | | | | | ● |
| 48 hr. | N | N | N | N | N | N | N | N | N | N |

N = No reaction
○ = Erythema
● = Edema
◉ = Edema and Erythema not measured separately

Scale • = 5mm.

Fig. 2

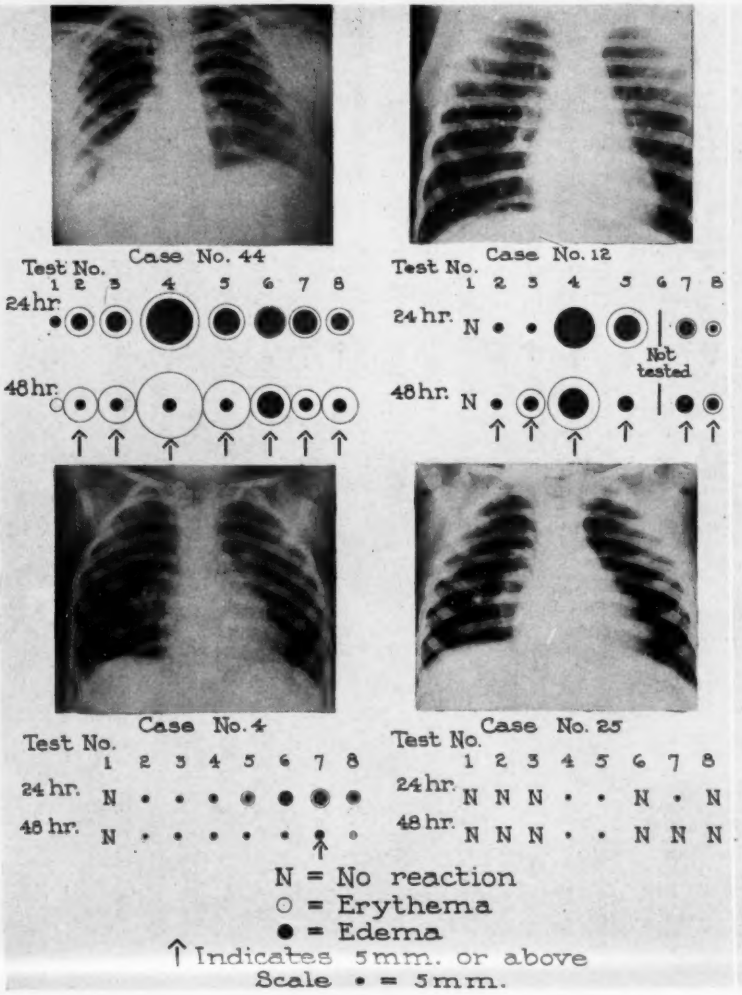

Case No. 44
Test No. 1 2 3 4 5 6 7 8
24 hr.
48 hr.
Case No. 12
Test No. 1 2 3 4 5 6 7 8
24 hr. N
48 hr. N
Not tested
Case No. 4
Test No. 1 2 3 4 5 6 7 8
24 hr. N
48 hr. N
Case No. 25
Test No. 1 2 3 4 5 6 7 8
24 hr. N N N N N
48 hr. N N N N N
N = No reaction
○ = Erythema
● = Edema
↑ Indicates 5mm. or above
Scale • = 5mm.

Fig. 3

Fig. 2

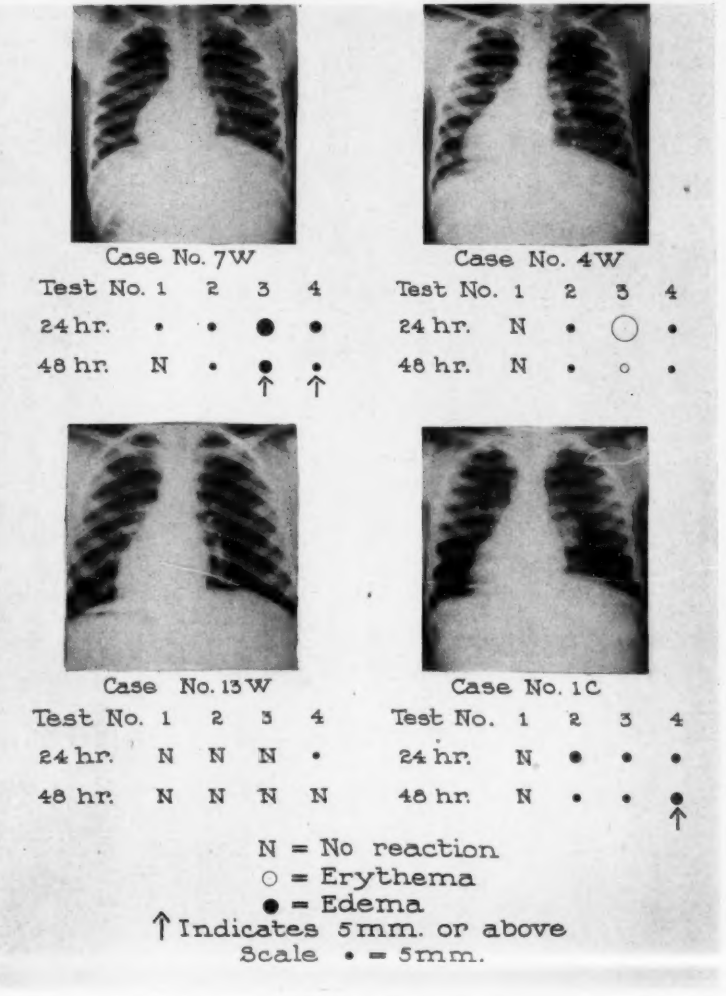

Case No. 7W
Test No. 1 2 3 4
24 hr.
48 hr. N
Case No. 4W
Test No. 1 2 3 4
24 hr. N
48 hr. N
Case No. 13W
Test No. 1 2 3 4
24 hr. N N N
48 hr. N N N N
Case No. 1C
Test No. 1 2 3 4
24 hr. N
48 hr. N
N = No reaction
○ = Erythema
● = Edema
↑ Indicates 5mm. or above
Scale • = 5mm.

Fig. 4

Fig. 1

Table 1 shows the relationship between the tuberculin reactions and the roentgenological evidence of calcification. Examples of some of the roentgenograms together with schematic drawings of the tuberculin reactions are shown in figures 1, 2, 3 and 4. Other observers have called attention to the waning of allergy (reaction to tuberculin) following healing of a tuberculous lesion and our observations seem to be further evidence that the allergic state may be at a very low level when the tuberculous lesions have become calcified. Whether an equally low state of allergy may exist with noncalcified lesions, as for example, in very young children who have small tuberculin reactions without roentgenological evidence of intrathoracic tuberculosis, can only be suggested. An incompletely calcified lesion is shown in figure 4, case 1C. The tuberculin reaction in this type of lesion is usually marked. In this instance, however, there was no response whatsoever to the first injection of tuberculin, and not until the fourth test was there a reaction of sufficient size to be considered positive.

No definitely active or progressive tuberculous lesions were detected in any of the groups nor were those children retested who had strongly positive reactions in the initial test. Thus, in this study there is no direct evidence of actual decrease in the allergic state of the individual child, as described by such observers as Johnston (2) and Krause (3), nor of any relationship between the degree of the cutaneous reaction to tuberculin and the extent and activity of the tuberculous lesion as suggested by Ayman (4) and others.

The only conclusion that can be drawn from these observations is that low grade or healed tuberculous lesions in children may exist when the tuberculin reaction is negative or only questionably positive following the intracutaneous injection of tuberculin in amounts up to 0.005 mgm. of P.P.D. and 0.1 cc. of 1:100 O.T.

## REFERENCES

(1) Nelson, W. E., Mitchell, A. G., and Brown, E. W.: Possibility of sensitization to tuberculin, Amer. Rev. Tuberc., 1938, *37*, 286.

(2) Johnston, J. A., Howard, P. J., and Maroney, J.: Quantitative study of tuberculin reaction in childhood tuberculosis, Ibid., 1934, *29*, 652.

(3) Krause, A. K.: Human resistance to tuberculosis at various ages of life, Ibid., 1925, *11*, 303.

(4) Ayman, D.: Intracutaneous quantitative tuberculin test in diagnosis of active tuberculosis, Jour. Amer. Med. Assn., 1934, *103*, 154.

# THE DIAGNOSIS AND TREATMENT OF TUBERCULOUS TRACHEOBRONCHITIS[1,2]

WADSWORTH WARREN, ARTHUR E. HAMMOND
AND WILLIAM M. TUTTLE

Clinical medicine is often slow to grasp the observations of the pathologist and turn them to its use. There is probably no more salient example of this truth than the fact that for long years tuberculous tracheobronchitis has remained a textbook legend.

Two years before the discovery of the causative agent of tuberculosis by Koch, Eppinger (1) fully described lesions occuring in the trachea and bronchi of persons who had died of tuberculosis. Relatively little was written of this complication until 1904, when it was again described in the German literature by Hedinger (2). In more recent years, Reichle and Frost (3) have described tuberculous lesions of the trachea and bronchi in autopsy material.

In two excellent papers, stenotic lesions of the trachea and bronchi occurring in cases of pulmonary tuberculosis have been discussed by Eloesser (4). The bronchoscopic appearance of tuberculous lesions within the tracheobronchial tree has been described by Ballon (6) and Samson (7). Since then, Barnwell, Littig and Culp (8), and Samson (9) have studied the symptoms presented by their patients and these have been reported; and Burgher, Littig and Culp (10) have published an excellent paper on the occurrence of such lesions in 122 autopsies performed on proved cases of pulmonary tuberculosis.

## INDICATIONS FOR BRONCHOSCOPY

The work of these investigators has demonstrated the usefulness of the bronchoscope as an adjunct in the diagnosis and treatment of pul-

[1] From the Department of Otolaryngology and the Department of Surgery (Division of Thoracic Surgery), Wayne University College of Medicine, and the Thoracic Surgery Service of Dr. E. J. O'Brien, Herman Kiefer Hospital and Wm. H. Maybury Sanatorium, Detroit Department of Health.

[2] Presented in part at a session of the 32nd annual meeting of the American Sanatorium Association, Milwaukee, Wisconsin, May 31, 1937.

monary tuberculosis. For a number of years, bronchoscopic examinations were made only on those cases where definite evidence of obstruction to the air passages existed. Slowly its use has been extended as more definite indications for its use have become understood. The writings of Clerf (11) and Jackson (12) have done much to dispel the fear of bronchoscopy in the tuberculous, once held by many.

The indications at present considered sufficient to warrant bronchoscopic examination in pulmonary tuberculosis are mainly those which have been previously described by Barnwell. Symptoms of obstruction were, and still are, the commonest indications for this diagnostic procedure. Such symptoms may, of course, vary widely, but it has been our experience that bronchial and tracheal partial obstruction are commonly manifested by dyspnoea out of proportion to the amount of pulmonary disease or to the degree of collapse, wheezing, difficulty in raising sputum, or persistent cough, with or without large amounts of sputum.

It is well to bear in mind that partial obstruction to an airway may be present without X-ray evidence of atelectasis, and this is especially true of tracheal stenosis. The converse of this statement is also true, namely, that complete stenosis may be present without symptoms, and X-ray evidence of atelectasis may be the only sign. Complete, or practically complete stenosis in the presence of pneumothorax with complete collapse of the lung may manifest itself only when reëxpansion of the collapsed lung is found impossible.

While signs of bronchial obstruction may, in the main, be the most constant cause of symptoms which demand bronchoscopic treatment, we, like others, have found that variations in amount and character of the sputum raised are often helpful symptoms in the diagnosis of tracheobronchial tuberculosis.

Considerable variation in the amount of sputum raised from day to day generally is indicative of partial obstruction along the tracheobronchial tree. However, we have found that it may also denote the presence of bronchial ulceration without marked obstruction. Large amounts of sputum, which may be mucoid rather than purulent, have been seen by us in a number of patients. When such symptoms have persisted, they have been considered sufficient indication for bronchoscopy. The presence of positive sputum, or sputum which is alternatingly positive and negative in the face of apparent control of the pulmonary parenchymal lesion or of complete absence of parenchymal dis-

ease, has been, in our series of cases, a strong indication that bronchial or tracheal ulceration exists.

Haemorrhage, when there is definite evidence of parenchymal disease which is not controlled by adequate collapse, is, of course, not an indication for bronchoscopy, unless it be to aspirate blood which is obstructing the air passages, and this is seldom indicated. However, where haemorrhage or streaking occurs in the absence of sufficient pulmonary disease to explain adequately the source, or where the control of parenchymal disease is adequate, we have felt that examination of the trachea and bronchi for ulcerations is definitely a desired procedure.

Recently, Samson and McIndoe (13) have performed routine bronchoscopic examinations on all patients admitted to the Michigan State Sanatorium. While this has been productive of most interesting data and has given rise to no ill effects, still we cannot feel that routine examination is a procedure to be recommended in all hospital admissions. We have taken but one exception to this stand against routine bronchoscopic examination. We believe that all candidates for thoracoplasty should be bronchoscoped as a part of the preoperative work-up. For such a procedure, however, there is good reason. In the past three years, three cases on whom thoracoplasties had previously been done have returned with severe symptoms of dyspnoea and inability to raise sputum. Examination has revealed the presence of tracheal stenosis in one, and stenosis of the contralateral main bronchus in the other two. Stenoses such as these are almost certainly on the basis of previous tuberculous involvement of the trachea or bronchi. At present, two of these patients are dead, and one, while still living, is a hopeless invalid. If the condition of the bronchus had been known in these cases, thoracoplasty would never have been done, as obviously it was only an added load to the patient and a futile gesture in the face of a situation which was already hopeless. Likewise, the presence of stenosis on the side where thoracoplasty is contemplated, while not a contraindication to thoracoplasty, is a condition of which the surgeon should be cognizant, for it is often necessary to dilate and aspirate while the lung is being collapsed. Furthermore, the presence of bronchial ulceration may give rise to sputum containing acid-fast bacilli and may cause the surgeon to sacrifice much good lung by further thoracoplasty in the thought that, because the sputum is positive, the cavity is not closed.

For these reasons, we have performed routine bronchoscopic examinations on all candidates for thoracoplasty during the year (table 4).

### INCIDENCE OF TUBERCULOUS TRACHEOBRONCHITIS

From a series such as the one here presented, it is impossible to state how frequently bronchial tuberculous ulcerations do occur. Samson and McIndoe, in the series of cases mentioned above, found ulcers in approximately 10 per cent of all cases. In a group of 90 patients at the Herman Kiefer Hospital and Maybury Sanatorium who had been advised to have thoracoplasty, twelve cases were found to have bronchial ulcerations, an incidence of 13.3 per cent (table 4). Likewise, in a group of 108 patients selected for bronchoscopic examinations because they presented symptoms of bronchial disease, 62 were found to have ulcerations or stenosis, or both, an incidence of 57.4 per cent (table 4).

When the incidence in a very accurate series, involving cases of all classifications such as those of Samson and McIndoe, is compared with our prethoracoplasty group, there would seem to be fairly good reason to believe that, in the far advanced or moderately advanced case, an incidence of from 10 to 15 per cent is not far afield.

### THE RESULTS OF BRONCHOSCOPIC EXAMINATION

The results presented here are a tabulation of the types of lesions present in 74 patients with tracheobronchial tuberculosis found during the past twelve months. The exact number of the respective types is shown in table 1. It will be seen that the majority of these ulcerative lesions fall into two types, namely, the discrete ulcer and the granulating ulcer.

The discrete ulcer is a well limited area of erosion, and its borders are sharp. It may vary in depth from a fraction of a millimetre to several millimetres, depending on its location and the thickness of the bronchial wall. In general, the margins are not or only very slightly raised above the level of the surrounding mucosa. The base is smooth, but occasionally gives the appearance that small tufts of granulation tissue are growing there. The color varies from bright red to deep violet. Such ulcers may occur anywhere within the tracheobronchial tree, but are more often located in the main bronchi, and in our series, not especially along the posterior wall as reported by Burgher, Littig and Culp, but rather about the orifices of the various lobar bronchi. They appear as single ulcers and are generally not close together, and thus do not tend to coalesce.

The granulating ulcer stands out as an entirely different type of lesion. The borders are not clear cut but tend to fade through a halo of oedematous mucous membrane into the normal mucosa. The base is composed

of numerous tufts of extremely friable granulation tissue. These may not rise above the surface of the surrounding normal mucosa, or may be elevated several millimetres above it. The color is a bright red except in cases where the granulations are exuberant; in such instances the tips of the granulation tufts may be grayish-white, and the base may vary from brilliant red to purple. The tendency of these lesions to bleed is notable, and only slight brushing with the bronchoscope may set up bothersome oozing.

The granulating type, in our experience, has occurred most commonly about the orifice of the main bronchi, on the carina and in the lower portion of the trachea. Whereas the discrete ulcer appears to represent a well resisted type of infection which advances slowly, the granulating type often advances rapidly, either throughout the extent of the bronchus first involved, or across the carina to invade the uninvolved bronchus. When seen in the trachea it may completely surround this struc-

TABLE 1

*Types of lesions found in 71 cases of tuberculous tracheobronchitis*

| | |
|---|---|
| Discrete ulcers | 22 |
| Granulating ulcers | 25 |
| Stenosis healed | 7 |
| Stenosis unhealed | 9 |
| Tuberculoma | 4 |
| Diffuse redness | 4 |

ture, and if the growth of the granulation tissue is high, it may partially occlude it.

Two types of stenosing lesions have been noted, and, as classified in table 1, have been called healed and ulcerating. The healed stenosis, it would seem, represents a healed ulcerative lesion in which the reparative process has partially or completely occluded the lumen. The surface is smooth and the reduced lumen is often covered with a pale mucous membrane. It occurs most commonly at the entrance of the main bronchi and in the lower trachea.

The ulcerostenosis represents, we believe, a stage midway between the healed, cicatricial stenoses and the granulating ulcer. The lumen is reduced, and from the inner wall of the stenosing band, easily bleeding, necrotic, tufted granulations protrude. Stenosis may be marked, quite as marked as in the healed type, for the protruding granulations often completely occlude the lumen.

The tuberculoma or tuberculous granuloma has been observed in this series in four patients. It represents undoubtedly, as tuberculomata do in other sites, a well localized lesion due to a high host resistance. In our experience it has occurred most frequently about the main bronchial orifices or near the orifices of the secondary bronchi. In general, they are globular tumor masses appearing not unlike carcinomata or benign adenomata of the bronchus.

Isolated tubercles are occasionally seen as small yellowish-white nodules beneath the mucosa.

In three patients there was a diffuse hyperaemia of the bronchial mucosa with moderate mucosal oedema. There are no clear-cut grounds for the assumption that this is a tuberculous lesion other than that in two patients the sputum was positive, and each had no other demonstrable lesion to account for the tubercle bacilli. When these lesions cleared, the sputum became negative in each case.

These areas of ulceration within the trachea and bronchi have been called tuberculous by the clinician because they occur in tuberculous individuals, and because of their resemblance to lesions discovered at autopsy which have been proved by microscopical sections to be tuberculous. We have performed biopsies in fourteen patients where the lesion was large enough to safely obtain tissue for study. In four instances, the lesions were tuberculomata, and in ten, were of the granulating ulcer type where the growth of granulation tissue was great enough to obtain a bite. The biopsies obtained from the four patients where a tumor mass was present were all tuberculous granulomata. The remaining biopsies taken on cases where a granulating ulcer was present showed tubercles in four of the ten cases.

The fact that the incidence of biopsies positive for tuberculosis was much less in the cases where biopsy consisted of granulation tissue tufts is not surprising. Such experience is common in biopsies of tuberculous granulation tissue even when the biopsy is large. In two instances it was necessary to take tissue on two occasions before positive evidence of the tuberculous nature of the tissue was established.

There is no evidence to date that removing small pieces of tissue from these lesions has led to any untoward results. There has been no attempt to remove tissue for study where the ulcer is of the discrete type or in the granulating type where the granulations are low. It is felt that the danger of perforating the bronchial wall in these cases outweighs the value of the additional information obtained by biopsy.

The following protocols illustrate some of the points brought out in the paper.

## CASE REPORTS

*L. K.*, case no. 13315: The patient was a thirty year old white female, single, who was first admitted to the Herman Kiefer Hospital on October 6, 1933, with a history of having been hospitalized in another hospital for pulmonary tuberculosis since January, 1933, at which hospital she had had a right phrenicectomy after pneumothorax had failed. She gave a history of positive sputum in June, 1933, and the result of sputum examinations prior to that time were not definitely known. She dated the onset of her illness from October, 1932, at which time she developed a cough and pain in the chest, loss of strength, and increasing dyspnoea. There was contact with a friend who was known to be tuberculous.

On physical examination, positive findings were limited to the chest. On the right side there was impaired resonance in the upper one-third with moderately coarse râles over the same area. On the left a few râles were heard in the first interspace anteriorly. The sputum was positive for tubercle bacilli on admission.

An X-ray film of the chest showed a moderately advanced tuberculous process of mixed type involving the apical region on the right, small areas of rarefaction on the right with a dense pleural shadow over the apical region. The left side was relatively clear, but there were a few scattered infiltrations of the productive type in the first interspace.

She was diagnosed as having moderately advanced pulmonary tuberculosis.

Right thoracoplasty had been advised prior to her admission to Herman Kiefer, and she was transferred to this hospital for that purpose. First-stage right thoracoplasty was carried out October 12, 1933, following which sputum became negative and cavity appeared closed and therefore no additional surgery was advised. She was transferred to Maybury Sanatorium for convalescence on February 27, 1934, but left that institution against advice in April, 1934. At subsequent examination in November and December, 1934, after several months of activity, the sputum was again positive. She was hospitalized for a brief time because of this positive sputum, but since the X-ray showed no change she was permitted to go home. She left the city for a time but returned in July, 1935 with a history of having had a positive sputum in April, 1935 with an increasing amount of sputum and some toxicity. X-ray examination at that time revealed a small area of rarefaction just below the clavicle on the right side and therefore additional surgery was advised.

Second-stage thoracoplasty was carried out July 25, 1935, and third stage September 12, 1935, and a Gale operation was done on October 8, 1935.

Sputum remained positive but the patient was again transferred to Maybury Sanatorium for convalescence in January, 1936. Since the sputum remained positive with apparent closure of the cavity, bronchoscopy was advised to determine the possible source for positive sputum. The first examination was February 12, 1936, at which time the right main bronchus was found to be entirely filled about the periphery with numerous tuberculous lesions which were, however, more numerous on the posterior wall. Prognosis was thought to be very poor and the bronchoscopist reported this as the most extensive bronchial tuberculosis that had been seen up to date. She was treated four times from February 12 to April 14, 1936, at which time the areas of ulceration appeared practically healed and inasmuch as the patient reacted poorly to bronchoscopy further examination was advised against. Whereas all sputum examinations except one were positive following the fourth-stage thoracoplasty, since treatment of the tuberculous tracheobronchitis was instituted, there was only one positive sputum, to June, 1936, at which time she was transferred to Maybury Sanatorium for further convalescence.

*L. C.*, case no. 16019: The patient was a twenty-nine year old white female. She was admitted to Herman Kiefer Hospital the first time January 28, 1936, giving a history of cough, haemoptysis, and night sweats since November, 1935, at which time she had developed a productive cough associated with a head cold. Three weeks prior to admission she had a haemoptysis of about one dram of bright red blood, following which she noticed increased fatigue. An X-ray film was taken at that time in the Out-Patient Department and hospitalization advised.

The physical findings were limited to the chest, where there was impaired resonance in the upper one-third on the right side, with harsh sounds, and a few moderately coarse râles above the second rib. On the left side breath-sounds were harsh in the upper one-third but no definite râles were heard. The sputum was positive for tubercle bacilli at the time of admission.

The X-ray examination of the chest (figure 6) showed: Right lung: There are dense exudative infiltrations in the upper third of the lung. There is an area of rarefaction at the first interspace. It is somewhat indistinct in outline and suggests a small excavation. The remainder of the lung is clear. Left lung: Some fibrosis in the infraclavicular region. The lung is otherwise clear. Conclusion: Moderately advanced tuberculous process, mostly exudative in type, involving the upper one-third of the right lung and a small area in the infraclavicular region on the left.

The diagnosis was moderately advanced pulmonary tuberculosis.

Right artificial pneumothorax was attempted but was unsuccessful. Right phrenicectomy March 20, 1936, with good elevation and immobilization of the diaphragm. Right artificial pneumothorax was again attempted in Octo-

ber, 1936, but was again unsuccessful and a right thoracoplasty was advised. First stage was carried out November 17, 1936. Second and last stages December 8, 1936, six ribs being removed, effecting an apparently satisfactory collapse of the involved lung area with no residual cavities (figure 7).

Sputum remained positive and the patient was therefore bronchoscoped December 30, 1936, at which time an area of ulceration was found in the medial lobe spur on the right main stem-bronchus. This was cauterized with the actual cautery. At the time of the bronchoscopy on February 3, 1937, the site of the previous ulcerated area appeared healed but another small area of ulceration was present in the left main bronchus on its medial wall. This area was cauterized. There were three subsequent examinations and treatments and at the time of the first examination April 14, 1937, all areas of ulceration formerly seen appeared to be completely healed (figure 8).

All sputum examinations were positive prior to the first bronchoscopic examination. There have been two positive results since that time, one from a routine examination and the other from a concentrated pooled sputum, the last of which was January 24, 1937, all examinations being negative since that time. Sputum culture made in March, 1937, was also negative.

*M. P.*, case no. 17196: The patient was a twenty-two year old single female office worker, who was admitted to the Herman Kiefer Hospital January 11, 1937, complaining of cough of eight months duration. She stated that she had pneumonia in October, 1936, and was in bed for three weeks. The cough was productive, from the onset, of a white mucopurulent material and occasionally this was blood-streaked. The right kidney had been removed at seventeen years of age (indication unknown).

On physical examination there was a right nephrectomy scar and no other positive findings except those related to the chest. Diminished excursion of the right hemithorax. Impaired resonance in the lower one-half on the right side. No râles or definite cavity signs. Left lung clear. The sputum findings were positive for tubercle bacilli on admission. The last positive sputum was March 25, 1937.

The X-ray examination of the chest (figure 1) showed: Right lung: There is an area of partial consolidation involving mainly the inner and middle lung fields at the base. There is a small area of rarefaction suggesting a beginning excavation. The remainder of the lung is clear. Left lung: Clear throughout. Conclusion: There is an increased density at the right base as described, indicating a moderately advanced tuberculous process.

The right phrenic nerve was crushed February 11, 1937, with good elevation and immobilization of the right hemidiaphragm (figure 2).

Bronchoscopy was done March 24, 1937, because of the unusual nature and location of the lesion and a continuously positive sputum which could not be

explained adequately on the amount of parenchymal disease present. The mucosa of the right main bronchus was injected and protruding from the middle lobe bronchus on the right there was a pinkish tumor about the size of a small pea. A biopsy of this was taken and the area cauterized with 30 per cent silver nitrate (figure 3). Sections of the biopsy material contained large numbers of acid-fast bacilli collected in clumps in the portions of the tissue in which degeneration was most marked, thus sustaining the presumptive diagnosis of tuberculous tracheobronchitis (figure 4).

There have been three subsequent bronchoscopic examinations with cautery of the involved area with 30 per cent silver nitrate or the actual cautery, each examination showing considerable improvement. Sections of a small bit of pedunculated material removed April 24, 1937 showed healing with fibroblasts, young fibrous tissue cells and numerous small blood vessels (figure 5). No tubercle bacilli were found. The sputum is now negative and the cough has disappeared.

*A. P.:* The patient, a white female of twenty-five, was admitted to Herman Kiefer Hospital in September, 1935. She gave a history that she had been well until a few months before admission, at which time she had what she thought was a rather severe cold. It was accompanied by cough and sputum and, when these did not subside, she consulted her physician.

Physical examination was essentially negative. X-ray examination of the chest at that time showed: Right lung: There were many calcium deposits in the apical region, and at the hilum. The remainder of the lung was clear. Left lung: There were a few productive infiltrations at the first and second interspaces and dense calcium deposits near the root.

The patient was classified as having minimal pulmonary tuberculosis.

The sputum examination showed tubercle bacilli on three occasions.

In November, 1935, a left phrenic crushing was done, and she was transferred to Maybury Sanatorium. In January, 1936, left pneumothorax was started because the patient's sputum was positive. This pneumothorax was continued to date. Sputum examinations had been positive on ten of thirteen examinations between November, 1935, and February, 1936. Because the patient's lung was very much collapsed, and there was a high negative pressure in the pleural cavity, it was considered probable that there was some obstruction in the bronchus. On January 21, 1937, a bronchoscopic examination was done, and showed very extensive ulceration extending to 2 cm. below the larynx down to and surrounding the left bronchial orifice. Another examination on February 4 showed marked improvement, and at each bronchoscopic examination there has been more and more improvement. Bronchoscopic examination on May 6 showed all the ulcers healed except one small area of redness on the anterolateral wall of the trachea above the left main bronchial orifice. There

was still about 80 per cent stenosis of the left bronchus. Sputum examination February 13 was negative by smear and concentration, but positive on culture. Smears, concentrations and cultures on three occasions since have all been negative. Patient's cough is much less and general condition is improved.

### TREATMENT OF TUBERCULOUS TRACHEOBRONCHITIS

Tuberculous tracheobronchitis is a new clinical disease entity. As far as we know, little has been offered in the way of treatment in any of the groups of clinical cases previously reported. Barnwell has reported nine cases in detail. A later report (15), at press when this paper was written, states that five of these patients are dead. Burgher, Littig and Culp are responsible in their article for the statement that the mortality in a group of cases having tuberculous tracheobronchitis was 47 per cent within one year after diagnosis was made. They further state that, "since the appreciation of the occurrence of these lesions, the diagnosis has been made in 33 cases; of these, bronchoscopy has been done in 24 cases, while in the rest the clinical signs have been so prominent as to make the diagnosis a practical certainity. In this group only one patient can be said to have shown any improvement; the others are already dead, or progressing steadily downward."

Deep X-ray therapy has been used as a method of treatment in a few cases by the Tuberculosis Unit and the Department of Radiology at the University of Michigan Hospitals, Ann Arbor. In view of Burgher's statement of the facts, this treatment has done little to check the progress of the disease. In our patients, an attempt has been made to ascertain the value of various types of cautery and local treatment to these areas. The report of results is based on the treatment of 57 cases of bronchial ulceration treated in the past two years.

Three methods of local treatment have been used. The actual live-wire cautery was first used in view of the favorable results which it had given in the treatment of laryngeal tuberculosis and lingual and buccal tuberculosis. The results obtained from this method were good, but the technical difficulties of manipulating a red-hot wire, which did not cool at once when the current was shut off, offered certain disadvantages; while no difficulties arose from its use, fear that it might caused its abandonment in favor of the Kernan cautery,[3] coupled with the Bovie Electro-Surgical unit, using a low coagulating current. Silver nitrate in varying dilutions has also been used. However, within the past year, a

[3] This instrument is made by The George P. Pilling & Son Co., Philadelphia.

solution of 30 per cent silver nitrate has been used. It appeared that this strength gave the best results. The majority of the cases reported have been treated with the last two mentioned methods.

As will be seen by referring to table 2, the results obtained by these methods of treatment have been gratifying.

Table 3 represents the cases which had positive sputum, despite the fact that there was no evidence of active or uncontrolled parenchymal disease. Twenty-two of the twenty-six healed cases now have negative sputum on direct smear and twenty-four hour concentrated specimens, while four cases have healed ulcers with a consistently positive sputum.

TABLE 2

*Results of treatment*

| | | |
|---|---|---|
| Total cases | 57 | |
| Ulcers healed | 34 | |
| Ulcers unimproved | 10 | (2 dead) |
| Ulcers under treatment | 9 | |
| Refused treatment | 2 | |
| Too ill for treatment | 1 | |
| Result unknown | 1 | |

TABLE 3

*Conversion of sputum in 31 cases in which ulcerations were the only apparent source of tubercle bacilli*

| | |
|---|---|
| Total number of cases | 31 |
| Sputum negative after ulcer healed | 22 |
| Ulcer healed but sputum still positive | 4 |
| Still under treatment | 5 |

The four cases with tuberculomata were all treated by removal of the tumor mass with biopsy forceps. After this was done, the base of the lesion was cauterized with silver nitrate or the electrosurgical current. It was often necessary where the tumor mass was large to remove small portions of it on several occasions, cauterizing the base of the lesion each time.

The results accomplished by this means have been good. There has been complete healing of the lesion in the four cases. When the lesion was healed, the base generally became covered with mucosa of normal appearance. Where the base was broad, the resultant healing left a puckered whitish scar.

While there has been a fair volume of literature accumulated on the

diagnosis and treatment of bronchial stenosis, the present situation calls for treatment which has not fallen within the experience of previous investigators.

We still do not know what to do with the case of the ulcerating stenotic lesion other than to attempt to clear the existing ulcer. This attempt has been made in each of the nine cases contained in this series. There has been no effort to dilate such areas of stenosis for fear of reactivating the bronchial disease. It has been noted, however, that when the ulcer has healed the occlusion present is often less marked. Further study of a larger group of cases over a longer period will be needed to clarify this point.

The healed stenosis presents a separate problem and one which must be handled differently in each individual case. When the stenosis is causing no symptoms and thus apparently no trouble, it is probably

TABLE 4

*Results of bronchoscopic examinations performed on 198 patients*

| | |
|---|---|
| I. Routine Prethoracoplasty Bronchoscopy | |
| Number of cases | 90 |
| Number of ulcers found | 12 |
| Percentage incidence | 13.3% |
| II. Bronchoscopy in 108 Selected Cases of Pulmonary Tuberculosis | |
| Number of cases | 108 |
| Number of ulcers found | 62 |
| Percentage incidence | 57.4% |

useless to tamper with it. On the other hand, if the stenosis is the cause of retention of secretions with toxic manifestations or if it is within the trachea or the bronchus of the contralateral lung, treatment must be attempted.

We have found that, where the lumen of the stenotic lesion will permit, the use of bronchoscopes of increasing size as a dilating instrument has proved most valuable. There are distinct advantages to this method. The bronchoscope lumen affords a constant airway and channel for aspiration and this is extremely useful in patients whose respiratory reserve is low.

In other instances where the stenosing band is short, it has been possible to bite away the protruding scar tissue and cauterize the base. This manner of enlarging the lumen, when coupled with subsequent dilatation, has given good results.

When the bronchial lumen is very small, a new bronchial bougie designed by Steele (14) has proved useful.

Bronchoscopic examination and subsequent treatments, if indicated, have not led to any untoward results. There have been no fatalities directly attributable to bronchoscopy, and spread of the tuberculous pulmonary disease has occurred but twice in 198 individual cases. The average number of treatments needed to bring about satisfactory results has been 5.7 treatments per patient, and the interval between treatments has been from two to three weeks.

As time has gone on we have come to have certain opinions about the relative merits of the electrosurgical as compared with the chemical method of treatment. It appears that, for the small well limited discrete ulcer, the electrosurgical method has given better results, while in the granulating type better response has been obtained by the use of silver nitrate. This is undoubtedly due to the fact that silver nitrate when applied on a sponge stick will cover and cauterize a larger area with less trauma than the small, less easily applied cautery point. There has been a tendency to couple the two forms, as treatment advances. Thus the electrosurgical point would be used on the deeper lesions after silver nitrate had at previous treatments removed the excessive granulation tissue.

How do such lesions heal? This is a question which at present we are not capable of answering. It is known that the healed areas are covered at first with a thin, rather friable mucous membrane which gradually becomes thicker and apparently more scarred as healing progresses. When the ulcer is deep and there has been considerable dissemination into the deeper bronchial tissues the scarring is greater. Where the lesion is more superficial, healing may leave no scar and the area apparently becomes covered with normal mucous membrane. Case *M. P.* (figures 1 & 5) demonstrates the covering of the area from which a tuberculoma was removed, by a squamous-cell type of epithelium.

Once healing has taken place, it appears that it is quite permanent. We realize that to report a method of treatment in tuberculosis when some of the cases have been well but a few months is by no means the final statement. On the other hand, the importance of this subject and the encouraging results obtained by us in treating it, coupled with the fact that approximately one-fourth of the cases reported have been well for one year, have prompted us to report the work. Our experience in treatment has run over a period of two years, the first of which was concerned mainly with working out details and testing various methods.

SUMMARY

From the results here tabulated, we are unable to render the rather severe prognosis which has been given to date. In the total number of cases (71) reviewed, there have been six deaths. These we feel have not been due to the tuberculous bronchial ulceration but rather to the severity of the parenchymal lesion. Bronchial ulceration may be in some instances a manifestation of poorly resisted disease, but this certainly is not true in all cases, and response to treatment is gratifying.

It is undoubtedly true that in some instances at least such lesions heal spontaneously in time. While this may be true in some cases, case *L. K.* and case *A. P.* well illustrate that, where such lesions have been present, the sputum has remained positive for from two to four years and has only become negative when treatment was instituted and the ulcers became healed. Such examples go far to prove the tuberculous nature of these lesions and the value of treatment. If such lesions are left to heal spontaneously, at what price is such healing accomplished? When a lesion is treated relatively early, healing occurs and leaves little or no trace, but when the ulcer is old and deep, stenosis has already begun to develop, and stenosis, as we have stated earlier, is an irreversible process. Thus it would seem that the early institution of treatment is to be recommended. It would also appear that it is better to err on the side of performing a bronchoscopic examination upon a patient with a normal bronchus when the diagnosis is in doubt, than to leave the ulcer untreated.

CONCLUSIONS

1. A study of the results of bronchoscopic examination performed on 198 tuberculous patients is recorded.

2. In this group ulcerative or stenotic lesions of the bronchus or trachea were found in 71 instances.

3. Fifty-seven cases of tuberculous bronchitis or tracheitis have been treated; of this number, 34 healed, 10 progressed or did not improve, and 9 are still under treatment.

4. There were 31 patients in whom the sputum was positive in spite of apparent control of the parenchymal disease. In this group healing of the bronchial ulceration was followed by prompt sputum conversion in 22 out of 26 healed cases.

5. In our experience, tuberculous tracheobronchitis has responded favorably to treatment with electrosurgical and chemical cautery.

## REFERENCES

(1) EPPINGER: Klebs. Handbuch der pathol. Anat., 1880, Bd. 2, p. 293.
(2) HEDINGER, E.: Verhandl. d. dtsch. pathol. Ges., 1904, 7–8, 83.
(3) REICHLE, H. S., AND FROST, T. T.: Am. Jour. Path., 1934, *10*, 651.
(4) ELOESSER, L.: Bronchial stenosis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, *25*, 123.
(5) ELOESSER, L.: Bronchial stenosis, Jour. Thor. Surg., 1931, *1*, 194, 270, 373, 485.
(6) BALLON, D.: Bronchoscopy in the diagnosis of asthma complicating pulmonary tuberculosis, Ibid., 1935, *5*, 103.
(7) SAMSON, P. C.: Tuberculous tracheobronchitis, Amer. Rev. Tuberc., 1936, *34*, 671.
(8) BARNWELL, J. B., LITTIG, J., AND CULP, J. E.: Ulcerative tuberculous tracheobronchitis, Ibid., 1937, *36*, 8.
(9) SAMSON, P.: Tuberculous tracheobronchitis, in press.
(10) BURGHER, J., LITTIG, J., AND CULP, J.: Tuberculous tracheobronchitis. Its pathogenosis, Amer. Jour. Med. Sc., 1937, *193*, 515.
(11) CLERF, L.: Is bronchoscopy indicated in tuberculosis? Jour. Amer. Med. Assn., 1931, *97*, 87.
(12) JACKSON, C. V., JACKSON, C. L.: Bronchoscopy, esophagoscopy, and gastroscopy, ed. 3, Phila., W. B. Saunders, 1934.
(13) SAMSON, P., AND MCINDOE, J.: Personal communication.
(14) STEELE, J.: Personal communication.
(15) BARNWELL, J.: Personal communication.

FIG.

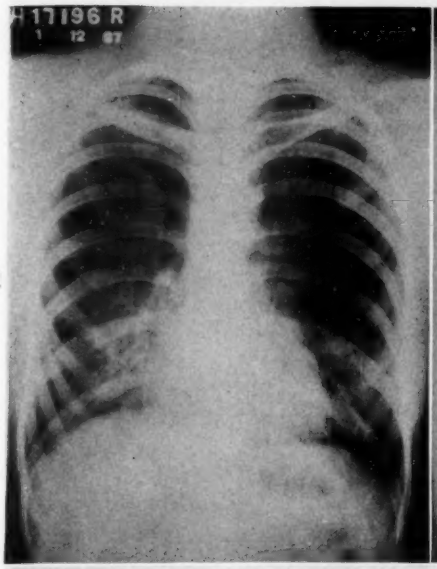


FIG. 1

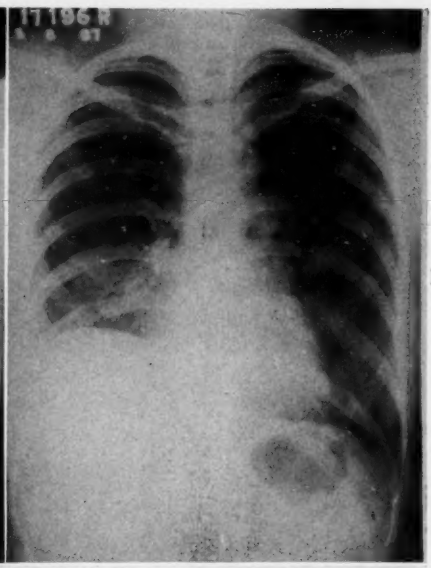


FIG. 2

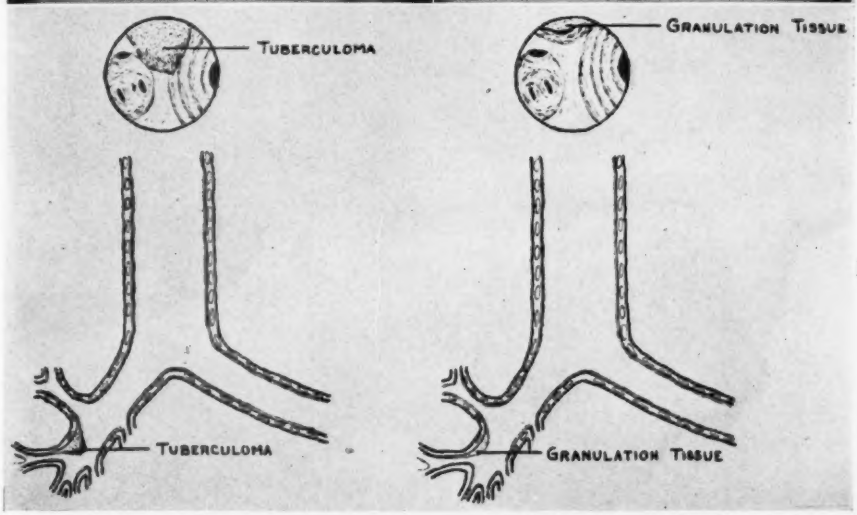



FIG. 3

FIG. 1. X-ray of case *M. P.* showing a basilar type of lesion. The sputum was consistently positive. A phrenic nerve crushing was done.

FIG. 2. Case *M. P.* X-ray after the phrenic crushing. The sputum was still positive. A bronchoscopic examination was advised because of the continued positive sputum in the absence of cavity.

FIG. 3. Case *M. P.* Schematic drawing of the appearance of the bronchial tree at the time of the first examination and after treatment. Note the presence of the tuberculous granuloma.

FIG. 4

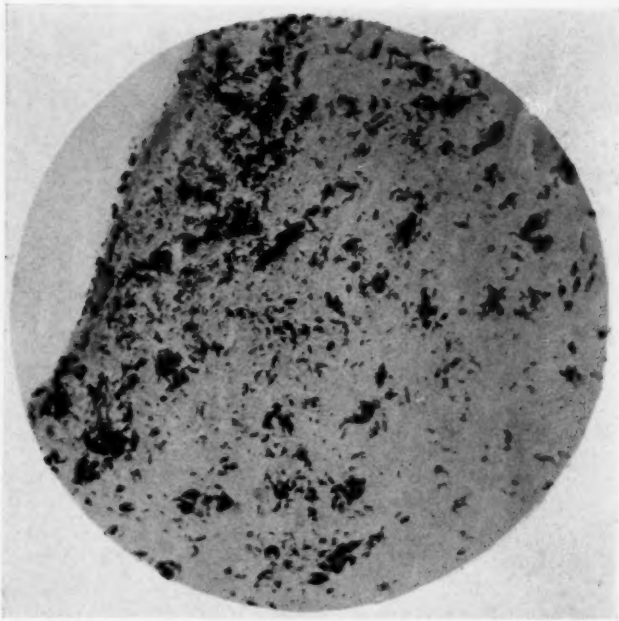


FIG. 5

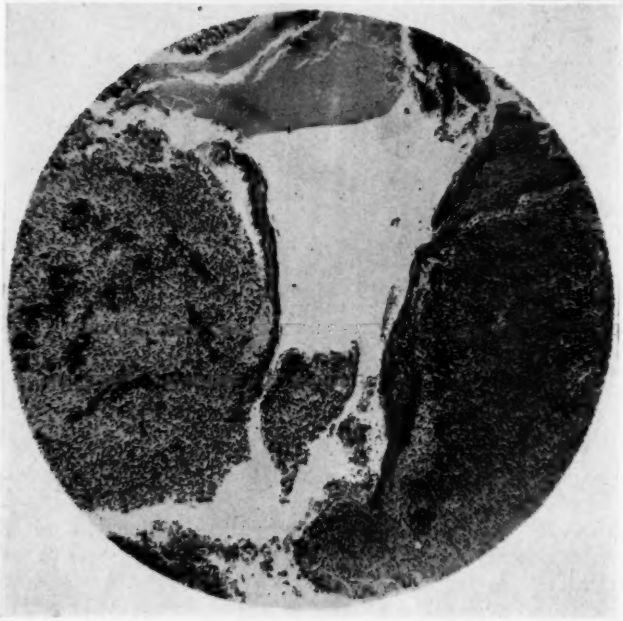


FIG. 4. A biopsy was taken of case *M. P.* Photomicrograph of the outer border of the biopsy stained with Ziehl-Neelsen stain. The dark clumps are masses of tubercle bacilli.

FIG. 5. A photomicrograph of a biopsy from the bronchus of case *M. P.* Five weeks after the original biopsy. Note the absence of tubercles and the presence of a thin squamous cell epithelium growing over the edges of the granulation tissue.

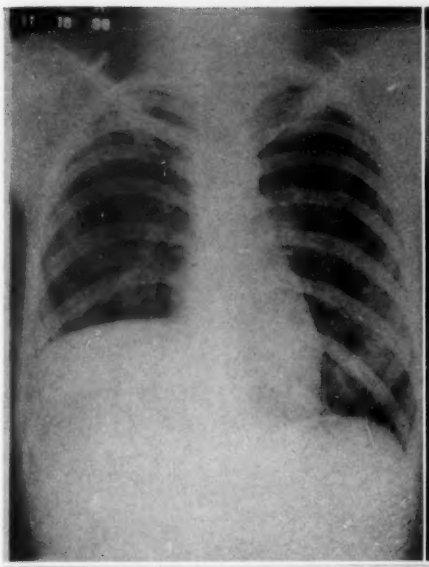


FIG. 6

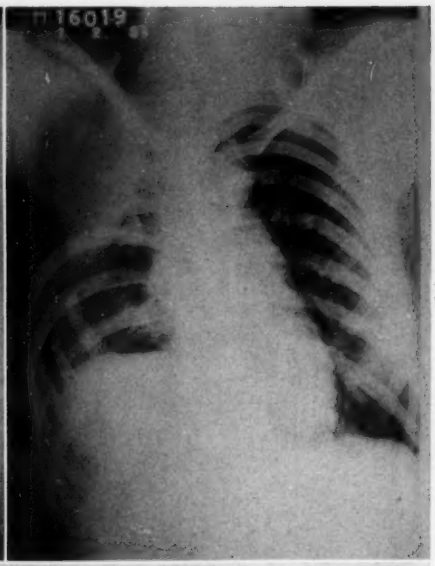



FIG. 7

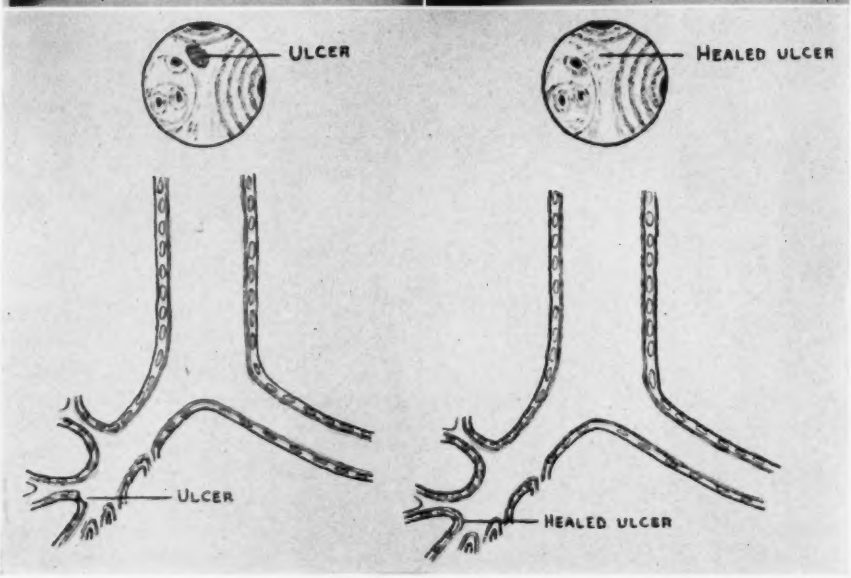



FIG. 8

FIG. 6. X-ray of case *L. C.* Pneumothorax had been tried but was unsuccessful. Phrenicectomy had been done, the cavity decreased in size but was still open. Thoracoplasty was advised.

FIG. 7. X-ray of case *L. C.* after a two-stage thoracoplasty had been done. The sputum was still positive although the cavity was closed. Bronchoscopic examination was advised.

FIG. 8. Schematic drawing of the appearance of the bronchial tree of case *L. C.* Note the location of the ulcer and the appearance after treatment. Sputum is now negative on culture of a seven-day pooled specimen.

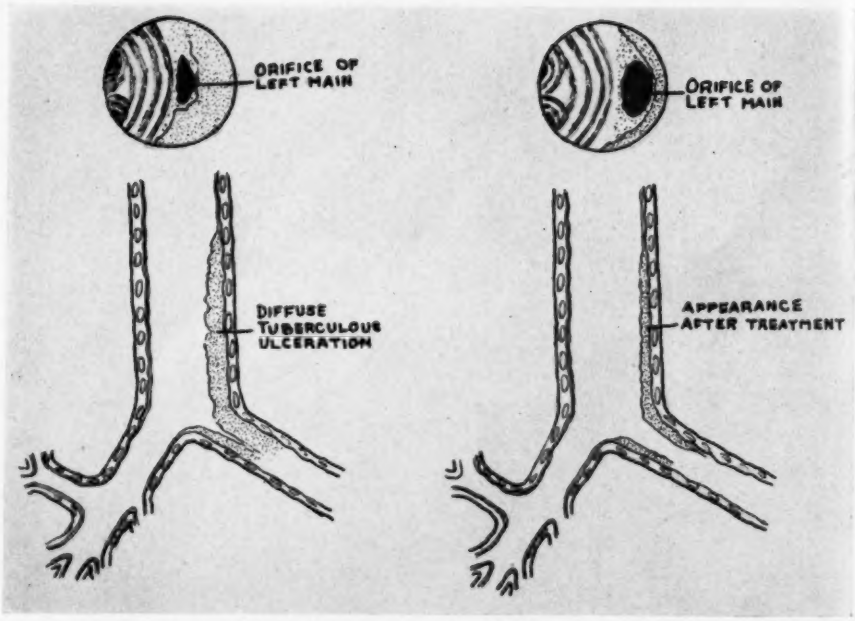



FIG. 9. Case *A. P.* This lesion was treated with 30 per cent silver nitrate with subsequent clearing of lesion.

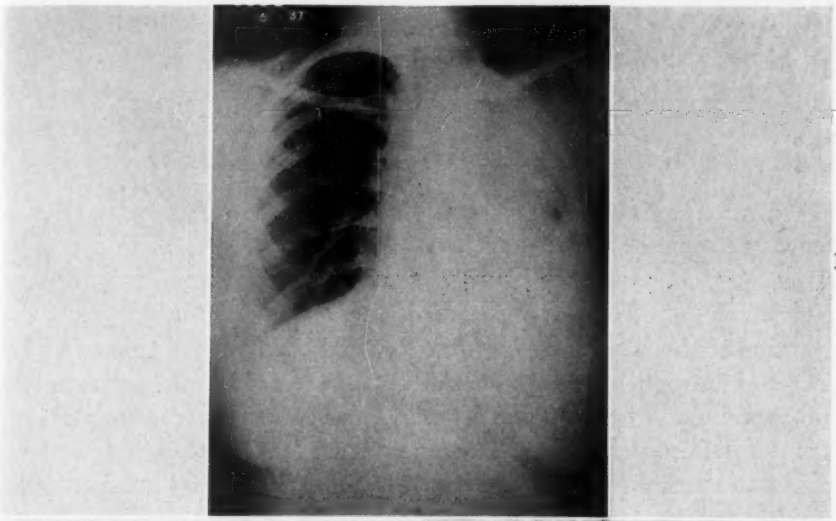


FIG. 10

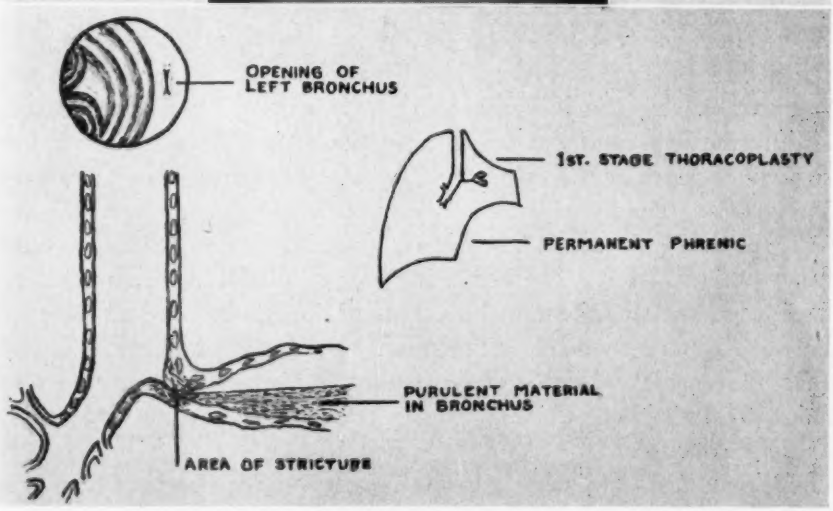



FIG. 11

FIG. 10. X-ray of the chest of a patient who two years before had had a first-stage thoracoplasty. Some difficulty in raising sputum was present at that time. The patient was bronchoscoped and a tuberculous lesion of the bronchus was found. Thoracoplasty was delayed. No treatment was instituted.

FIG. 11. Schematic drawing of the bronchial tree of the case whose X-ray is shown in fig. 10. Two years before, the bronchus on the left side had been patent. Bronchoscopy was advised at this time because of inability to raise sputum and the presence of a low-grade temperature elevation. Note the almost complete stenosis at the site of the previous bronchial disease.

# BRONCHIAL FACTOR IN CAVITATION[1, 2]

SIDNEY J. SHIPMAN

From time to time in the history of any disease the discovery or development of some new means of investigation appears to have the most far-reaching consequences. This has been especially true in the history of tuberculosis. The development of percussion by Auenbrugger, the invention of the stethoscope by Laennec, the discovery of tuberculin by Koch and its application by means of the skin test of Pirquet immediately come to mind. These advances, while by no means all or even, perhaps, the most important of the discoveries marking forward steps in the development of our knowledge of tuberculosis, nevertheless have proved to be of continued and ever-widening effect.

How much credit should be given any man in the acknowledgment of such a discovery is, of course, problematical. At certain periods the stage seems to be set for advances along specific lines. In a large measure this is so in the present wave of investigations which have as their object the clarification of our knowledge of the state of the bronchi in pulmonary tuberculosis. The more general use of the bronchoscope, for which due credit should be given to Chevalier Jackson and his group, has no doubt been a potent factor. The increasing use of lipiodol has been another. These, together with the more liberal use of the fluoroscope and roentgen film, have apparently done much to clarify a group of problems in clinical tuberculosis which have long been thorns in the side of many an able clinician. Quite independently, many observers have been arriving at the same conclusions.

For many years clinicians have been observing the effects of bronchial tuberculosis with or without stenosis. It is doubtful, however, if many appreciated even remotely the tremendous significance prior to the appearance of Eloesser's classical papers in 1932 and 1934 (1, 2). Indeed,

[1] Presented at a session of the Clinical Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

[2] From the Department of Medicine and the Thoracic Surgery Clinic, University of California Medical School, San Francisco, California.

so careful and complete were Eloesser's observations, so clear and convincing were his descriptions of the symptoms and physical signs, and so abundant the wealth of clinical material he presented that subsequently it has been unnecessary to do more than refer to his papers as far as a description of the condition is concerned.

Eloesser, however, appeared to be chiefly concerned with stenosis. This is at times a late development and one associated with healing. To some it seemed that the important thing might be to detect early tuberculous bronchial lesions with the hope of influencing them, so that subsequent stenosis would not occur, in the same sense that it is desirable to detect early pulmonary lesions or intestinal or laryngeal lesions to prevent the development of undesirable late effects.

Accordingly, with the coöperation of Dr. Jesse Carr, of the Department of Pathology of the University of California Medical School, an examination of autopsy material was made to determine the frequency of tuberculosis in the bronchi which lead from cavities present at death. In approximately 10 per cent tuberculous changes could be demonstrated. Some involvement of the bronchial wall which produced partial stenosis was commonly found. Although we were concerned primarily with early tuberculous changes, the excellent studies of Salkin, Cadden and McIndoe (3, 4) have served to elucidate the manner in which cavities may be blocked by numerous other conditions.

Granting the truth of these findings, which appeared to be indisputable, it seemed that a possible explanation for the not uncommon observation that patients are sometimes made worse by pulmonary collapse might be made. For example, those administering pneumothorax refills are occasionally confronted with the sudden clouding of an involved lobe, with or without symptoms. Increased compression accentuates the condition; partial expansion appears to relieve it. This is the effect of bronchial blockage. The same phenomenon seems to follow phrenicectomy or thoracoplasty at times. Orthodoxy, then, or proceeding by rule of thumb from bed-rest to pneumothorax to phrenicectomy to thoracoplasty, playing one card rapidly after another, as the saying goes, may not always be beneficial but may at times be positively harmful.

A noteworthy example is the following case.

*J. B.*, a man of 28, whose family history and past history were unimportant, but whose wife had broken down with pulmonary tuberculosis several years before and who was at the time a pneumothorax patient, developed cough,

expectoration and slight afternoon elevation of temperature. This was in 1926. On examination he was found to have infiltration and cavitation of the right upper lobe. The sputum contained tubercle bacilli. Refusing the usual sanatorium or home care, he continued working, but was persuaded to modify his activities and enlarge his caloric intake. He gained weight and within three months fluoroscopic examination revealed no cavity. Meanwhile his sputum and other symptoms disappeared. Subsequently he refused all invitations to be examined until January, 1935, when, his symptoms having reappeared, a film showed infiltration and cavitation of both upper lobes (figure 1). Pneumothorax was instituted on the right side and the patient was kept strictly in bed, but with little improvement. Subsequent films showed healing of the original cavity on the left side, with formation of a new one behind the left first rib. Pneumothorax was accordingly instituted on the left side and continued on the right. The right phrenic nerve was crushed. Aside from a gain of 30 pounds in weight there was no essential change in the patient's clinical condition and a film taken in October, 1935 revealed two cavities in the right upper lobe and one in the left (figure 2). Thoracoscopy on the right revealed no adhesions which might have been expected to interfere with cavity closure. The mediastinum, curiously enough, appeared to be drawn slightly toward the right.

Meanwhile, however, one striking phenomenon occurred. After each refill the patient appeared to be worse, both subjectively and objectively. So critical did his condition become that it was believed some change in therapy was necessary. Consultations with numerous internists and thoracic surgeons brought forth suggestions ranging from thoracoplasty on the right to thoracoplasty on the right and intrapleural pneumonolysis on the left. The patient then solved his own problem by becoming so ill that any further procedure was quite out of the question and the bilateral pneumothorax was abandoned with the hope that if he improved at all something else in the way of collapse therapy might be considered at a later date. Then, to our great surprise, he promptly recovered. Within two months his sputum disappeared and he was symptom free. Fluoroscopy revealed no shadows suggestive of cavitation and a film taken in September, 1936 showed only a slight fibrosis of the right apex, slight pleural thickening at the right base and a shift of the mediastinum toward the right (figure 3).

Here was what seemed to be a paradoxical phenomenon in which bilateral compression not only failed to close cavities on either side, but actually made the patient worse.

Such occurrences are not fortuitous; there must be reasons underlying the appearance of these phenomena, which it is the urgent duty of the

FIG. 1 FIG. 2 FIG. 3

FIG. 1. Cavitation in both upper lobes before collapse.

FIG. 2. With collapse of right side first, then left, two cavities appear in the collapsed right upper lobe, one small one behind the junction of the left first rib and its costal cartilage. Patient clinically worse with collapse.

FIG. 3. Reëxpansion with coincident cavity closure on both sides. Fibrosis of right upper lobe and deviation of mediastinum toward right. Patient symptom free; negative sputum.

clinician to discover. In the case of *J. B.* it seemed that an adequate explanation might be offered as follows:

A reference to figure 4A shows both lungs expanded, with two cavities in the right upper lobe, one in the left. Figure 4B reveals the right upper

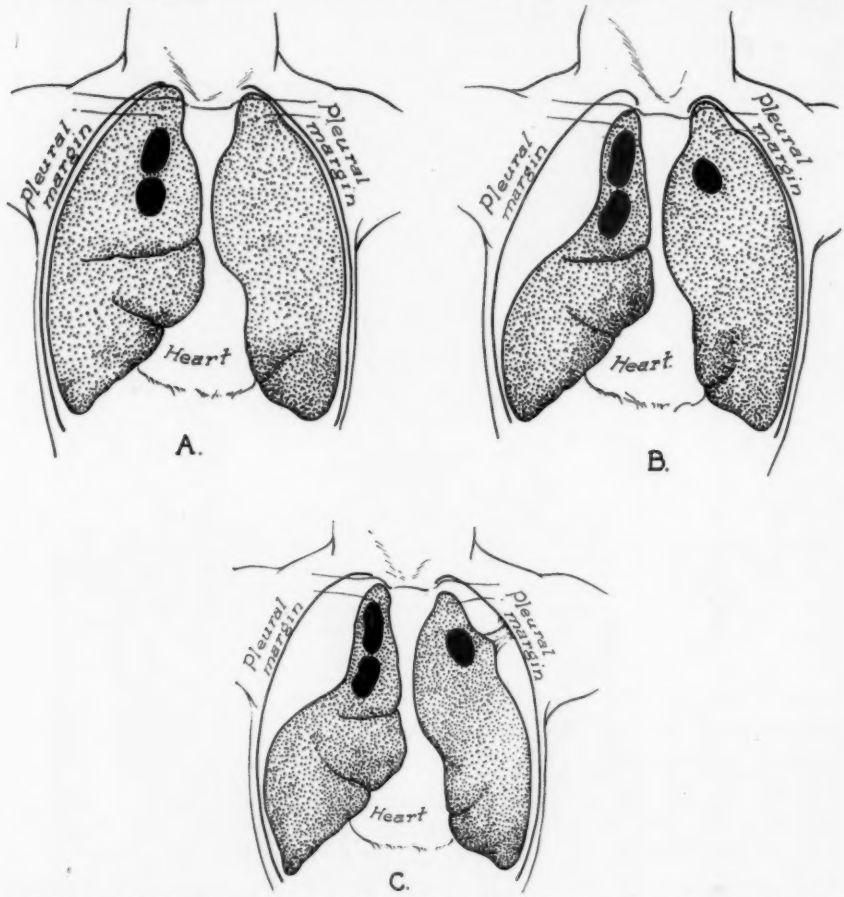



FIG. 4. (A) Diagrammatic illustration of lungs in case *J. B.*, just prior to collapse of right upper lobe. (B) Following collapse of right upper lobe, with fresh cavitation in left upper lobe. Note there is enough surrounding lung tissue in (A) to occupy position taken up by cavities in (B). (C) Bilateral compression with three cavities, undiminished in size. Pleural adhesion over cavity in left upper lobe.

lobe compressed and a fresh cavity in the left upper lobe. Figure 4C reveals both upper lobes compressed, the left being held out somewhat by an adhesion, the condition being essentially that appearing in figure 2, the roentgenogram of October 22, 1935. If, also, bronchi draining these cavities are assumed to be tuberculous and therefore of narrowed lumen,

the condition of the right upper lobe may be illustrated diagrammatically by figure 5. If no bronchial obstruction exists there is sufficient normal lung tissue to occupy the space cavitated if even a 50 per cent compression of the upper lobe is obtained. The actual compression secured was much greater than this, as can be seen by reference to the roentgenogram of October 22, 1935, or figure 4C. Nevertheless, the cavities did not close and the patient was made worse by compression.

FIG. 5

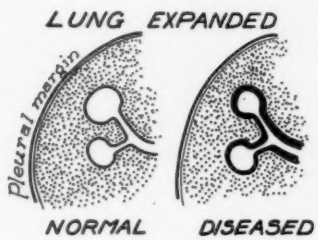
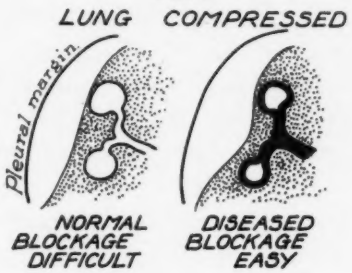



FIG. 6



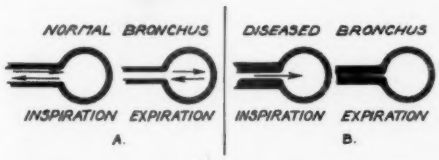




FIG. 7

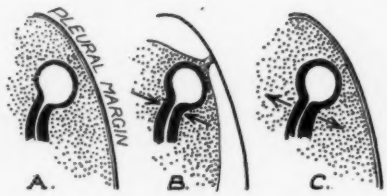



FIG. 8

FIG. 5. An enlarged schematic drawing illustrating narrowing of bronchi when occupied by disease in uncompressed right upper lobe.

FIG. 6. Illustrating what may have happened in case *J. B.* with compression. Bronchial obstruction produced by compression.

FIG. 7. Diagrammatic illustration of check valve action in diseased bronchi. Diseased bronchial wall approximates during expiration, tending to keep cavities expanded.

FIG. 8. Diagrammatic illustration of what may have happened in left upper lobe in case of *J. B.* (A) Before compression. Bronchus narrowed by disease. (B) After compression, the force of which is exerted not only on cavity walls but also on bronchi, thus defeating the object of compression therapy. (C) With reëxpansion bronchial walls parted, cavity allowed to close.

Figure 6 illustrates what may be assumed to have happened if the bronchi were actually diseased when compression was instituted. The bronchial lumen was simply obliterated and no amount of surrounding lung capable of compensatory hypertrophy could avail to cause collapse. Upon reëxpansion it may be assumed that the bronchial block was relieved and collapse of the cavities followed through compensatory emphysema and mediastinal displacement in the usual manner.

Closure of the cavity on the left side, which also took place on reëxpansion, may also be explained by assuming the presence of tuberculous bronchitis. Here it is necessary to refer to the check valve action so often referred to by Jackson and others, and to assume that compression may exert its effect not only upon the cavity itself but upon the bronchus which drains it (figure 7). Here it is seen that a diseased bronchus, unlike a normal bronchus, may constantly tend to "blow up" a cavity, since air can enter easily but escapes with difficulty, for the bronchi expand and contract with respiration, as any bronchoscopist knows. Figure 8A shows diagrammatically how the left apex appeared expanded; 8B how force was exerted on the diseased draining bronchus, narrowing its lumen and tending to nullify any favorable effect of compression on the cavity itself; and 8C how reëxpansion may have acted in opening the lumen of the draining bronchus, allowing the cavity to close by means of compensatory emphysema in the surrounding lung. This explanation ignores the presence of the adhesion on the left side, which appeared to play no part in whatever occurred.

The above case is not unique, but is uncommon in that cavities in both upper lobes closed with the simultaneous abandonment of pneumothorax on both sides. The explanation offered may not be the correct one, but seemed the most logical in view of all the circumstances. If it were correct, it seemed to suggest that the method of attack in the attempt to close certain cavities should be not so much collapse therapy but rather the cure of diseased bronchi draining such cavities and the attempt to relieve obstruction.

Previous apparent success in the treatment of hyperplastic bronchial tuberculosis by means of general irradiation with ultraviolet light produced by the hot quartz burner suggested that a method offering some hope of success was at hand. The method was originally suggested because of its success in the treatment of intestinal tuberculosis and was employed in much the same manner, namely, by general irradiation until the skin became tanned. Its use in treating hyperplastic bronchial tuberculosis was first publicly suggested at a meeting of the California Tuberculosis Association at Sacramento in 1936, since which time several Californian workers have written that they have had some success with the method.

At any rate, it had been observed at the Thoracic Surgery Clinic of the University of California Medical School that bronchi previously beefy in appearance, with narrowed lumen, exquisitely tender and bleeding easily, had become pale and of more nearly normal size following general

irradiation of several weeks' to months' duration. That other, perhaps more logical, methods of treatment had been suggested (5) we were well aware, but they seemed to offer slight hope of success in these nebulous and more or less hypothetical cases.

Fifteen patients have been selected for this treatment, in which a positive or negative result may be said to have been obtained up to the present time. The criteria of selection were rigid and as follows: (*1*) Persistent localized wheezing over the cavity area must have been present, a presumptive sign of bronchial involvement. (*2*) A pneumothorax must have been tried, successful in all respects except that of cavity closure. (*3*) Thoracoscopy must have revealed no adhesions capable of preventing collapse.

TABLE 1

| CASE | SEX | AGE | LOBE | ONSET | PNEUMOTHORAX BEGUN | PNEUMOTHORAX ENDED | LAMP BEGUN | CAVITY CLOSED | TIME TO CLOSURE | REACTION |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *months* | |
| 1 | F | 44 | LU | 2–35 | 6–35 | No | 5–36 | 8–36 | 3 | 0 |
| 2 | M | 23 | RU | 3–36 | 5–36 | No | 9–36 | 11–36 | 2 | 0 |
| 3 | M | 30 | RU | 10–34 | 12–34 | No | 6–35 | 8–35 | 2 | + |
| 4 | M | 34 | RM | 1–35 | 3–35 | 3–36 | 10–35 | 1–36 | 3 | 0 |
| 5 | F | 30 | LU | 2–36 | 3–36 | No | 5–36 | 7–36 | 2 | 0 |
| 6 | M | 42 | RU | 2–36 | 4–36 | No | 6–36 | No | 6 | 0 |
| 7 | F | 25 | LU | 4–36 | 6–36 | No | 8–36 | No | 4 | + |
| 8 | F | 24 | LL | 6–36 | 6–36 | No | 8–36 | No | 4 | 0 |
| 9 | F | 31 | RL | 8–36 | 9–36 | No | 12–36 | 1–37 | 1 | + |
| 10 | F | 36 | RU | 6–36 | 8–36 | No | 10–36 | 1–37 | 2 | 0 |
| 11 | M | 38 | RU | 3–36 | 5–36 | No | 8–36 | No | 6 | 0 |
| 12 | M | 28 | RU | 12–34 | 3–35 | No | 6–36 | 7–36 | 1 | 0 |
| 13 | F | 29 | LU | 5–36 | 5–36 | No | 6–36 | No | 6 | + |
| 14 | M | 22 | RU | 5–36 | 5–36 | 3–37 | 10–36<br>1–37 | No | 4 | + |
| 15 | F | 35 | RL | 1–37 | 1–37 | 4–37 | 2–37 | No | 4 | 0 |

Note: Sputum positive in all cases before treatment, negative in all closed cases at present. Reaction to lamp treatment consisted of fever for a few days with collateral haziness about cavity by X-ray.

In establishing these criteria it was believed that the failure of collapse therapy to close the cavities could not be ascribed to extrabronchial factors, but must lie in the bronchi themselves. A further condition was laid down; namely, that the pneumothorax should be maintained at as nearly as possible constant pressure and collapse to obviate the factor of bronchial kinking influencing closure. As noted in the table, several

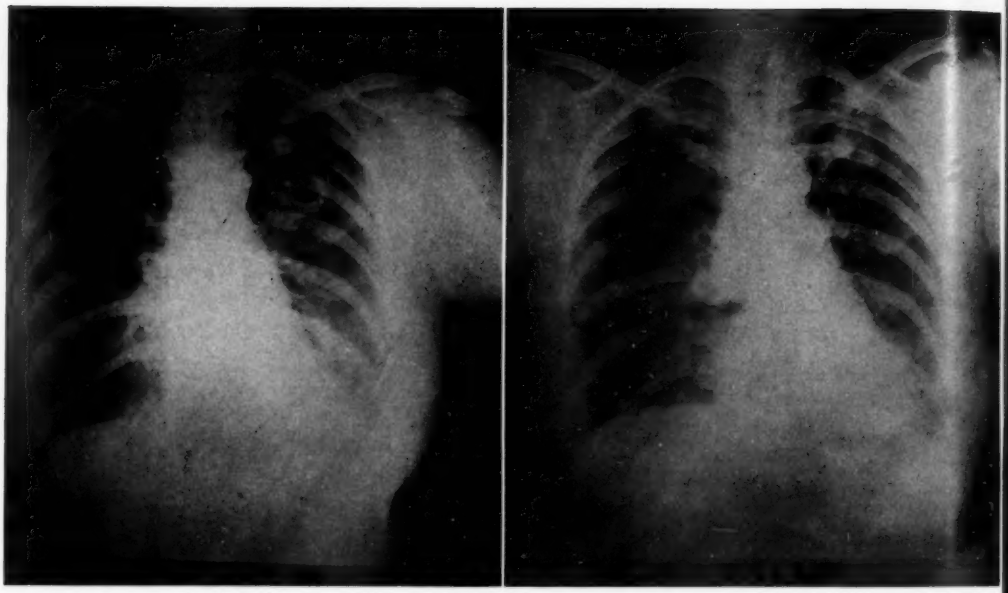


FIG. 9 FIG. 10

FIG. 9. Case 1 of table 1. Selective collapse left side. Open cavity left upper lobe. Sputum positive.

FIG. 10. Case 1 of table 1. Same degree of collapse maintained. Cavity closed following general irradiation with quartz lamp.

pneumothoraces were abandoned after the result of treatment appeared no longer in doubt.

Table 1 gives the result obtained in the 15 cases so chosen. In eight (53 per cent) the cavities closed; in seven (47 per cent) they did not. This is not an impressive percentage, but when it is considered that the patients selected were of that group, so puzzling and so baffling in the past, that one seemed to be at a dead end as far as therapy was concerned, it may not be without significance. Although several reactions were observed, as noted in the table, they were in all cases only transitory, lasting a few days, and apparently did no permanent damage. Naturally, it is difficult to get a large series which fulfills the above conditions.

## COMMENT

Collapse therapy has so occupied the attention of clinicians during the past two decades, particularly as far as cavity closure is concerned, that new points of view have been long overdue. There undoubtedly exists a not insignificant group of cavities in which closure may be influenced by factors other than pulmonary collapse, and in which the old rule of thumb (pneumothorax, phrenicectomy, thoracoplasty) is not applicable. This group constitutes to-day one of the most baffling clinical problems confronting the physician, a problem which urgently demands solution. The list of cases here presented is submitted not so much to recommend a method as to propose a new point of view, of which it is to be hoped there may be many in the future. An open mind in this matter is probably quite as important as an open bronchus.

For helpful counsel and for aid in following certain patients, my thanks are due the Thoracic Surgery Group of the University of California Medical School, Dr. Harold Brunn, Director.

## REFERENCES

(1) Eloesser, L.: Bronchial stenosis, J. Thoracic Surg., 1931–32, *1*, 194, 270, 373, 485.
(2) Eloesser, L.: Bronchial stenosis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, *30*, 2.
(3) Salkin, D., Cadden, A. V., and McIndoe, R. B.: The blocked pulmonary cavity, Ibid., 1936, *34*, 634.
(4) Salkin, D., Cadden, A. V., and McIndoe, R. B.: Postmortem bronchography, Ibid., 1936, *34*, 649.
(5) Samson, P.: Tuberculous tracheobronchitis, Ibid., 1936, *34*, 671.

# THE PROGRESSIVE PRIMARY COMPLEX[1,2]

OSCAR AUERBACH

It is well established that the initial tuberculous infection occurs as a nodule at the portal of entry and, together with its draining lymph nodes, runs a definite anatomical course. In the great majority of cases the primary complex goes on to anatomical healing. In a small number of cases, however, the primary complex goes on to progression. Despite the fact that this progressive primary complex has been observed in studies of the primary complex by Ghon (1), Ghon and Kudlich (2) and Blacklock (3), and of tuberculosis in sucklings by Moll (4), Ghon (5), Bergmann (6), Geipel (7), Hedren (8), Fischer (9), and Koch (10), it has hardly been investigated systematically. These investigators demonstrated that primary foci occurring in children under one year of age have a tendency to liquefy, whereas those occurring in children more than one year old usually go on to anatomical healing. Epstein (11) and Ghon (5) have applied the term "phthisical" to the form of cavitary tuberculosis in sucklings that develops from the primary infection and found that death in these cases results from pulmonary tuberculosis.

Most of the knowledge of the progressive primary complex thus far accumulated comes from Europe and consequently the patients studied have been predominantly white. In the Pediatric Tuberculosis Service at Sea View Hospital not only is it possible to observe a considerable number of cases, but both white and Negro children are seen and an opportunity is presented to make a systematic study of the progressive primary complex in both groups at autopsy.

This study covers seventeen cases autopsied in a period of four years. The age of the individuals ranged from nine months to nine years, with the highest incidence (fifteen cases) between the ages of one and three years. With one exception all were Negroes. At Sea View Hospital the proportion of colored children to white children at present is 5:4. This great preponderance of Negro over white emerges from

[1] Presented at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Department of Pathology, Sea View Hospital, Staten Island, New York.

a population where a reverse numerical ratio of Negroes to whites exists, and so one would expect to find in the hospital a fairly similar low ratio of Negro to white. Since, however, the reverse is true in this series, the implication would seem to be that the progressive primary complex is more prone to develop in the Negro than in the white.

Whether the massive infection which the progressive primary complex represents, and which we encounter so predominantly in the Negro child, is to be explained on the basis of the greater exposure of these children to large and continued doses of tubercle bacilli from an active case of pulmonary tuberculosis must be considered. But in this series, at least, this does not seem to have been an important factor. Although some of the children had been exposed to open cases of pulmonary tuberculosis, usually in the mother, nevertheless in eight instances no contact history of such exposure could be obtained.

### PULMONARY PRIMARY FOCUS

*Site:* Since the foci result from the aspiration of tubercle bacilli, they are observed in the well aerated portions of the lungs. The focus was always present in the subpleural aspects of the lobe, and one could actually observe its location before the lungs were opened. If the case comes to autopsy before liquefaction has occurred, a mass may be felt just beneath the pleura. After the occurrence of cavitation, however, the pleurae over the focus are depressed. In eight patients of this series the primary foci were located in the lower lobe, and in nine cases were situated in the upper and middle lobes. In nine cases the right lung and in eight the left lung was the seat of the primary focus.

*Cross appearance:* The size and appearance of the primary focus depend upon the stage of progression in which it is found. In this series it varied from 1.5 to 6 centimetres. A strikingly characteristic feature was the slight tendency to encapsulation and a strong tendency to liquefaction and cavity formation. In the early stage of progression the focus was smaller than the draining lymph nodes, whereas in the later stage of development the focus reached the same size and was even larger than the nodes.

The progressive primary focus observed at autopsy reveals a large, irregularly demarcated area of caseation, with no definite capsule. The lung tissue immediately surrounding this nodule is pneumonic in character and the pleura overlying the focus is thickened. This may be the result of a caseous pleuritis which has developed from the direct extension

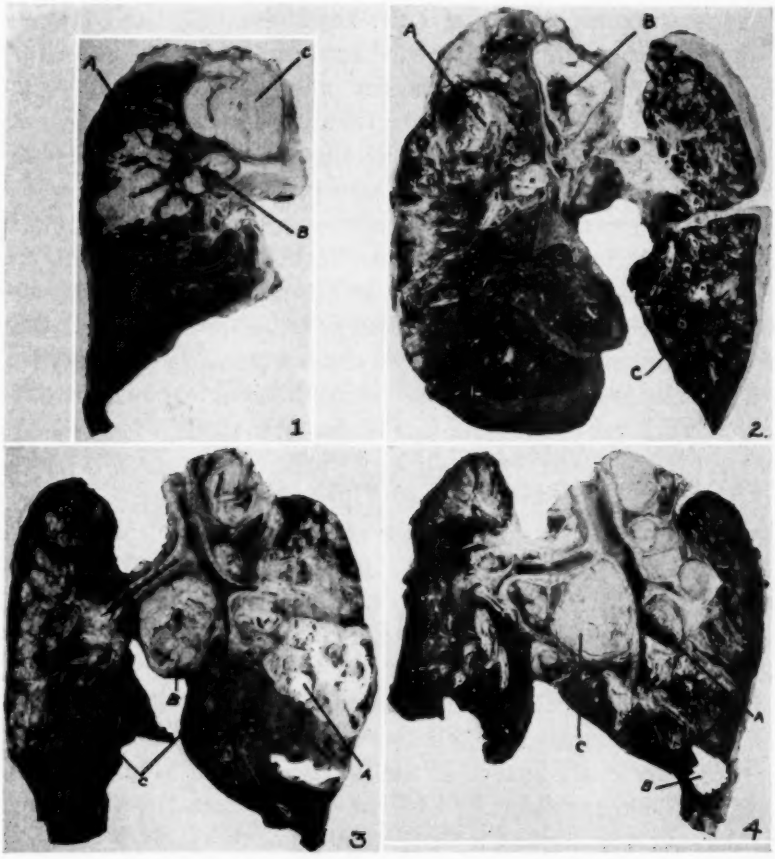



FIG. 1. The progressive primary complex in a male colored child, aged two years. The primary focus is present in the right upper lobe (A). The enlarged peribronchial (B) and the tracheobronchial (C) lymph nodes show the same stage of development as the focus.

FIG. 2. The progressive primary complex in a Negro male child, aged nine months. The primary focus (A) in the right upper lobe and the corresponding right superior tracheobronchial lymph nodes (B) are in the stage of liquefaction. Caseous foci (C) in the left lung are in part due to a bronchogenic and in part due to a haematogenous dissemination.

FIG. 3. The progressive primary complex in the stage of liquefaction in a Negro male child, aged one year. The focus in the right lower lobe (A) and the enlarged right inferior tracheobronchial nodes (B) show central liquefaction. There is a dissemination of foci (C) in the lower lobes.

FIG. 4. Rupture of a softened peribronchial lymph node into the right lower lobe bronchus (A) with the development of secondary cavitation (B) following the perforation. The regional lymph nodes (C) are enlarged and caseous. The patient was a Negro male child, aged two years.

of the focus, for when a caseous pleuritis develops it usually involves the pleura over the entire lung. Most often, however, there is only a localized fibrous thickening of the pleura overlying the focus.

In the later stages the area of caseation may progress to involve the greater part of a lobe, usually with liquefaction accompanying this extension, as in nine cases of this series. In one or more zones of the focus, softening of the caseous mass occurs and evacuation of the liquefied material results in an irregular shaggy excavation. This type of excavation, different from the tertiary cavity observed in isolated pulmonary tuberculosis, is designated the "primary cavity" (Schmincke (12)). Cavity formation in the primary focus occurs shortly before death so that the reparative process in the form of a productive reaction is not extensive. The capsule which forms the boundary of the primary cavity is not well defined, with large caseous masses forming the inner wall of the excavation and signifying incomplete liquefaction. Trabeculae, a constant finding in tertiary excavations, are usually absent in primary cavities.

Although Jaffé (13) speaks of the possibility of a primary cavity rupturing into the pleural space and causing a pyopneumothorax, such a complication was not observed in this series. The rarity with which this occurs is due to the fact that the primary focus does not reach the pleura and that it is the perifocal reaction which surrounds it that extends to the pleura resulting in a fibrinous and later a fibrous thickening of the pleura. However, if the focus extends to involve the pleura then liquefaction and cavity formation may result in a spontaneous pneumothorax with a subsequent pyopneumothorax.

The gross appearance of the remaining pulmonary parenchyma depends chiefly upon the stage of development of the primary focus. In all the cases in this series in which the focus did not go on to liquefaction there was evidence of haematogenous tuberculosis in the form of miliary, acinous and sublobular foci throughout the lung. But wherever primary cavitation was present, the lungs were studded chiefly with large foci in the form of sublobular and lobular areas of caseous pneumonia which were fused irregularly with the surrounding firm tissue and showed little tendency toward encapsulation. Central liquefaction and cavity formation are frequently observed in bronchogenic caseous pneumonic foci but once cavitation has occurred it is impossible to distinguish foci of bronchogenic origin from those of haematogenous origin.

Calcification was not observed in any one of the primary foci studied

in this series, confirming the findings of previous investigators. In four cases there was no active progression of the pulmonary foci, which measured from 1 cm. to 2 cm. in diameter, were circular in outline, and were surrounded by a gray capsule. They were well demarcated from the surrounding lung tissue. Progression was present, however, in the draining lymph nodes.

*Microscopical appearance:* The appearance of the focus is that of a large area of necrosis. The elastic fibres of the alveolar septa, vessels and bronchioles are intact within the zone of caseation, their presence identifying the focus as an original area of caseous pneumonia. The area of necrosis is surrounded by a narrow zone of granulation tissue, containing epithelioid and giant cells. Beyond this specific granulation tissue, the alveoli contain an exudate (perifocal inflammation) composed of serum, alveolar phagocytes and lymphocytes. The perifocal inflammation is extensive and occupies large areas of the lung. Liquefaction and cavity formation are similar in children and in adults and are the result of the action of the proteolytic enzymes digesting the caseous material. Liquefaction may take place in one or more areas of the caseation. With the expulsion of the liquefied material a cavity wall is present, the inner wall of which is composed of a wide area of caseation. In all finished cavities in adults, there is a third layer composed of fibrous tissue, but in children this is either not present or very poorly developed.

## THE LYMPH NODES OF THE PRIMARY COMPLEX

The efferent lymphatic system of the lungs drains into the lymph nodes of the hilum. The nodes most extensively involved are those lying along the course of the bronchi and in the angle between the trachea and bronchi. The paratracheal, cervical, posterior mediastinal and peripancreatic nodes are involved to a much lesser extent. Although caseation does occur in the lymph nodes of the contralateral side, most extensive involvement is found in the nodes on the side of the focus. They are matted together and often cause pressure on the surrounding structures such as the trachea, bronchus or blood vessels.

*Gross appearance:* The lymph nodes which extend from the focus to the tracheobronchial angle are extensively enlarged, completely caseous, and frequently have undergone central liquefaction. Although the nodes in the tracheobronchial angle most frequently show this change, liquefaction may occur in the peribronchial lymph nodes. Liquefaction of the lymph nodes, however, is not necessarily concomitant with

liquefaction of the primary focus. Softening occasionally occurs both in the focus and in the lymph nodes, but more frequently it occurs independently in one or the other.

The lymph nodes may rupture into the trachea, bronchi and blood vessels. In two cases of this series, a softened lymph node had perforated into a bronchus. In one instance a caseous pneumonia followed by cavitation ensued upon the rupture. In the other instance death (due to tuberculous meningitis) occurred too soon after the perforation for spread to occur through the bronchus. In each case it was a peribronchial node that had ruptured into the bronchus.

*Microscopical appearance:* The entire node showed extensive caseation and the caseous zone was surrounded by a narrow zone of specific granulation tissue. Calcium deposition was not observed in any node but the central zones of some nodes showed liquefaction, and in these areas there were dense collections of intact polymorphonuclear leucocytes.

### CHANGES IN OTHER ORGANS

Evidence of a haematogenous dissemination was present in every case. This generalization, which occurs while the primary complex is still fresh, has been designated by Huebschmann (14) as "early generalization" in contrast to "late generalization," which occurs after the primary complex has healed. The spleen was the organ in which the caseous haematogenous foci were most frequently present, although they were also present in the kidneys, adrenals and liver. The spleen was enlarged in all seventeen cases and was densely studded throughout with yellow nodules varying from 1 mm. to 1 cm. in diameter and even larger. Haematogenous dissemination consisting of large nodules is known as large nodular tuberculosis and the findings of a large nodular haematogenous tuberculosis in any case with a progressive primary complex is indicative of an overwhelming blood-stream infection. The incidence of haematogenous dissemination in this series was 100 per cent, which was greater than that reported by Hedren (8) (68.4 per cent over one year and 82.9 per cent under one year), and Ghon (5) (91 per cent). It is now generally accepted that haematogenous dissemination occurs not usually, but rarely as the result of the rupture of a caseous focus in the blood-stream (Huebschmann (14), Pinner and Kasper (15) and Rich and McCordock (16)). It is believed that it is the opening of the lymphatics into the venous circulation which results in the blood-stream dissemination, although, since the infection is most extensively present

in the lymph nodes, one would expect these to be the source of the entrance of the tubercle bacilli into the blood-stream.

*Tuberculous meningitis:* Nine of the seventeen patients died of tuberculous meningitis, whereas the remainder showed neither clinical nor pathological evidence of meningitis. Of the nine cases in which cavitation had occurred, four died as a result of a tuberculous meningitis. It is interesting to note that this finding does not confirm the observations of Epstein (11) and Ghon (5), who found that death resulted in such cases from the pulmonary lesions rather than from meningitis. The examination of the brains of those cases which expired as a result of tuberculous meningitis revealed the presence of tuberculomata in five instances.

*Gross changes in the gastrointestinal tract:* Tuberculous ulcerations were found in all cases in which cavitary tuberculosis was present in the lungs. The ulcers were extensive and occupied great portions of the small and large intestines. Their presence can be explained by the well established fact that the liquefied cheesy particles containing numerous tubercle bacilli are not expectorated by children, but swallowed. Geipel (7) believes that lack of resistance of the intestinal epithelium in children to the tubercle bacilli may also be a factor in the frequency of intestinal tuberculosis.

## CONCLUSIONS

1. The progressive primary complex was studied in a series of seventeen cases which came to autopsy.

2. Sixteen cases were Negro children, one was white, the age ranging from nine months to nine years.

3. Generalization in the form of large nodular tuberculosis was present in all the cases, and tuberculous meningitis caused the death of nine.

4. Cavitation with bronchogenic spread and extensive intestinal ulcerations, which were present in all cases with cavitary formation, are frequent complications of the progressive primary complex.

5. Progression and softening may occur simultaneously or independently in both the primary focus and the draining lymph nodes. In two cases a caseous node had ruptured into a neighboring bronchus.

## REFERENCES

(1) Ghon, A.: Über Sitz, Grösse und Form des primären Lungenherdes bei der Säuglings— und Kindertuberkulose, Virchow's Archiv f. path. Anat., 1925, *254*, 734.

(2) Ghon, A., and Kudlich, H.: Weitere Mitteilungen über die Tuberkulose bei Säuglingen und Kindern, Zeitschr. f. Tuberk., 1926, *46*, 391.

(3) BLACKLOCK, J. W. S.: Tuberculous disease in children, Medical Research Council, Special Report Series No. 172, London, 1932.
(4) MOLL, L.: Zur Tuberkulose im Säuglingsalter, Monatschr. f. Kinderheilk., 1924, *28*, 58.
(5) GHON, A.: Über kavernöse Säuglingstuberkulose, Zeitschr. f. Tuberk., 1925, *43*, 3.
(6) BERGMANN, H.: Cavernöse Lungentuberkulose beim Säugling, Berliner Klin. Wchnschr., 1915, *52*, 77.
(7) GEIPEL, P.: Über Säuglingstuberkulose, Zeitschr. f. Hyg., 1906, *53*, 1.
(8) HEDREN, G.: Pathologische Anatomie u. Infektionsweise der Tuberkulose der Kinder, besonders der Säuglinge, Ibid., 1912–13, *73*, 273.
(9) FISCHER, T.: Cavitation in the lungs in young infants, Lancet, 1912, p. 831.
(10) KOCH, M.: Kavernöse Lungenphthise bei einem 5 Monate alten Kinde, Verhandl. d. Deutsch. Path. Ges., 1906, p. 263.
(11) EPSTEIN, B.: Quoted by GHON (5).
(12) SCHMINCKE, A.: Das Kavernen Problem vom pathologischen anatomischen Standpunkt, Beitr. z. Klin. Tuberk., 1927, *67*, 124.
(13) JAFFÉ, R. H.: The pathology of pulmonary tuberculosis, Goldberg's Clinical Tuberculosis, vol. *1*, 1935, p. 97.
(14) HUEBSCHMANN, P.: Pathologische Anatomie der Tuberkulose, J. Springer, Berlin, 1928.
(15) PINNER, M., AND KASPER, J. A.: Pathological peculiarities of tuberculosis in the American Negro, Amer. Rev. Tuberc., 1932, *26*, 463.
(16) RICH, A., AND MCCORDOCK, H. A.: An enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hospital, 1929, *44*, 273.

# GENERALIZED NODULAR TUBERCULOSIS[1]

## Report of a Case Associated with Primary Carcinoma of the Lung

J. E. WELKER AND LEE H. LEGER

Tuberculosis of the liver as a terminal miliary lesion is found in from 50 to 80 per cent of tuberculous patients coming to autopsy (8). On the other hand, local tuberculosis, either as solid nodules or as abscesses, is extremely rare. The latter condition was first described by Bristow (2) in 1858 and since that time few cases have been reported.

The condition is characterized by multiple, irregular, white, firm nodules of various sizes which in some cases undergo softening to form tuberculous abscesses.

Rosenkranz and Howard (10) have classified tuberculosis of the liver into four types: "(*1*) terminal miliary tuberculosis; (*2*) miliary tuberculosis as a part of a generalized miliary tuberculosis; (*3*) local tuberculosis, either multiple tumor-like tuberculomas or abscesses; and, finally, (*4*) tuberculosis of the bile ducts or tubular tuberculosis."

Since the case to be reported here represents the local form, only this type will be discussed.

Felberbaum (4) in 1912 reported a case of nodular tuberculosis of the liver and in a review of the literature was able to find less than a dozen cases reported. Since that time we find the report of cases by Maximowitsch (7), deCrespigny and Cleland (3), Sheldon (11), Walker (12), and Goyle, Vasudevan and Krishnaswamy (5).

Morris (8) in 1930 reported a case of tuberculous abscess and found only eleven cases of abscess reported in the literature. Recently two more cases have been reported by Ariel (1).

Rosenkranz and Howard (10) made an extensive review of the literature and reported three cases of tuberculosis of the bile ducts. Two of these cases presented abscess formation but were not classified as a local form of tuberculosis of the liver.

The case reported here illustrates the difficulties of clinical and patho-

[1] From the Department of Pathology, University of Kansas School of Medicine and St. Margaret's Hospital, Kansas City, Kansas.

logical diagnosis. Clinically, this patient was considered to have either a cirrhosis or a malignancy of the liver. The pathological diagnosis was considered by everyone viewing the gross specimens to be a malignancy and unfortunately only a small amount of material was saved. It was only through microscopical study that the real character of the lesion was determined.

## CASE REPORT

*Fred R. K.*, a white male, age 63, entered the hospital August 17, 1936 with the complaints of dyspnoea and oedema. Illness began in June, 1936, with pleurisy lasting for two weeks, followed by dyspnoea and oedema. He had lost 35 pounds in the two months prior to admission.

Physical examination showed a poorly nourished white male with a barrel-shaped chest and sunken infra- and supraclavicular fossae. Expansion was diminished, especially on the left. Breath-sounds were diminished. The abdomen was enlarged and there was shifting dulness in both flanks. The margin of the liver was down about three fingers below the costal margin. There was oedema of the feet and ankles.

Blood cultures gave negative results. The Wassermann reaction was negative. The leucocyte count varied from 17,000 to 29,550 with 86 to 93 per cent polymorphonuclear leucocytes. The icteric index was 3.11. The urine analysis was persistently negative.

Roentgen examination revealed a left partial hydrothorax and the liver shadow was enlarged, displacing the stomach. Fluoroscopy of the stomach revealed no intrinsic lesion. Three weeks after admission patient developed chills and fever which continued until his death seven weeks later.

*Postmortem examination:* The peritoneal cavity contains about 4,000 cc. of clear straw colored fluid. The peritoneal surfaces are studded with firm white nodules varying in size from 1 to 15 mm. in diameter. The liver is enlarged and nodular and extends 6 cm. below the costal margin. The mesenteric and retroperitoneal lymph nodes are enlarged and some of them are firm while others are soft and show fluctuation. The left pleural cavity contains approximately 1,000 cc. of a straw colored fluid. Many adhesions are present. The pleural surface of the left lung is opaque, thickened and roughened by many firm white nodules varying from 2 to 15 mm. in diameter, and showing a tough caseous material in the centre. There is a large firm circumscribed grayish-white mass, 8 by 10 cm., involving most of the left apex. Also a smaller similar mass, 3 by 3 cm., is located in the left hilum. Both of these masses showed a tough homogeneous necrotic material on section. Scattered throughout the left lung are many miliary tubercles. On the pleural surface of the left lung in the lower lobe is a gray, spongy, well outlined nodule which

measures 2 cm. in diameter. It projects 1 cm. above the surface and has a very different characer from the other nodules on the pleural surface, being much more cellular and friable. The pericardial sac is thickened, opaque and is studded with tubercles. Many fresh adhesions are present. The liver

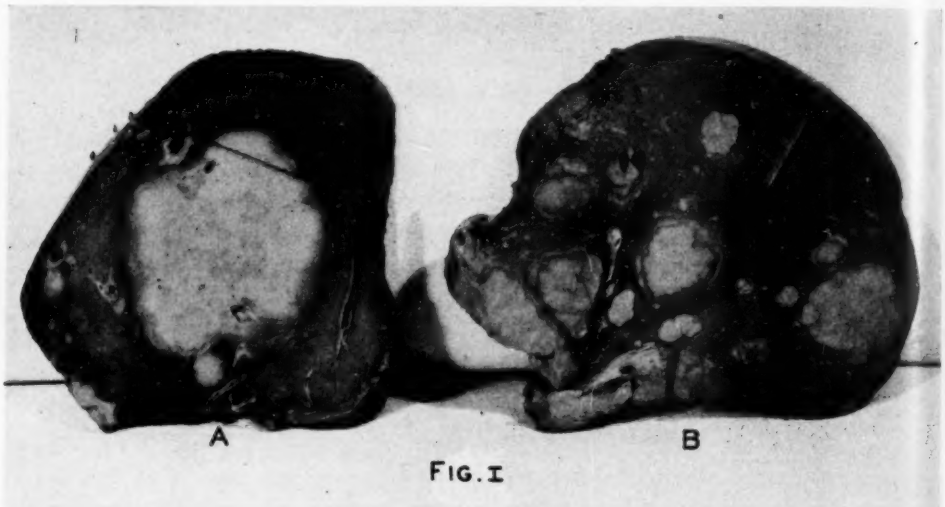



FIG. I

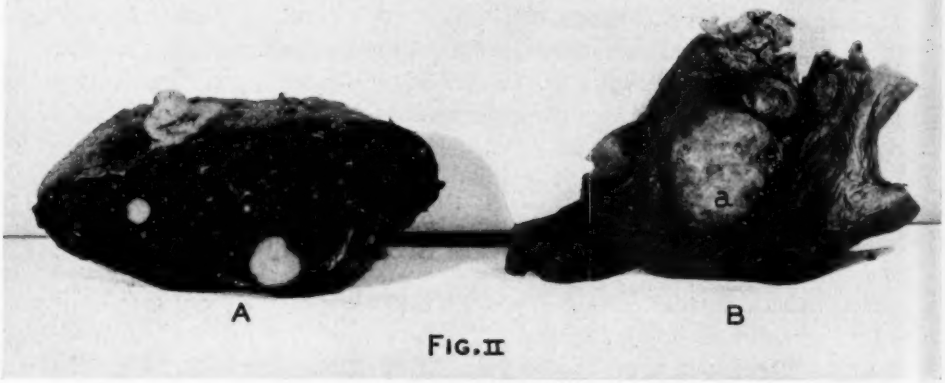



FIG. II

FIG. I. A: Cross section of liver showing large circumscribed tuberculous nodules. B: Same.

FIG. II. A: Section of spleen showing tuberculous nodules. B: Portion of lung showing carcinomatous nodules (a) surrounded by tuberculous nodules.

weighs 2,055 gm. The capsule is thickened and there are about 40 nodules visible on the surface. The smallest nodule being a mere speck while the largest is 7 cm. in diameter. There is no umbilication of the liver capsule about the nodules, which are grayish-white in color, firm in consistency and

are seen projecting from the surface. They are well outlined from the surrounding liver tissue. Throughout the cut section the liver tissue is found to have similar nodules, which cut with considerable resistance, appear to be encapsulated and resemble tumor masses. The centre of these masses is

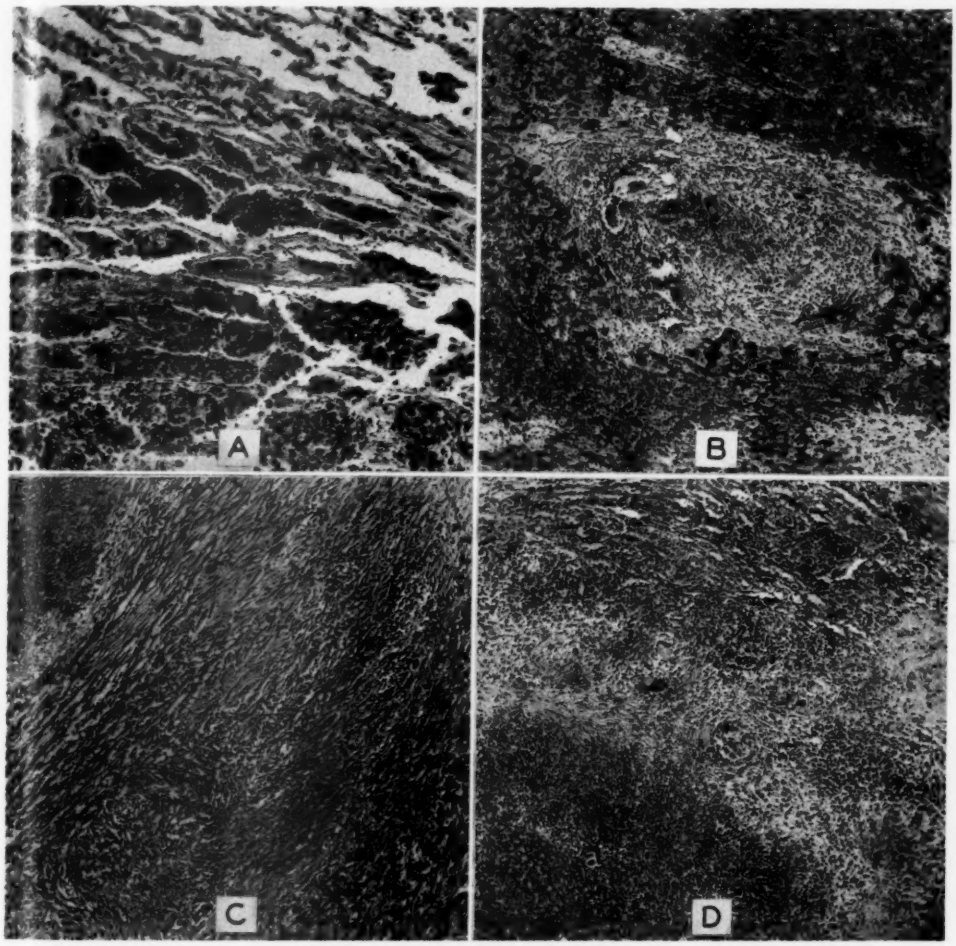



FIG. III. A: Microscopical section of undifferentiated carcinoma of lung. B: Section of liver showing small miliary tubercles. C: Section of liver showing edge of large caseous mass (a) surrounded by dense fibrous tissue and leucocytes. D: Section of spleen showing edge of a large caseous mass (a) surrounded by miliary tubercles with giant cells.

tough in consistency and not at all friable. Similar nodules may be seen on the surface and in the substance of the spleen and also in the left adrenal gland.

*Anatomical diagnosis:* Generalized nodular caseous tuberculosis affecting

the liver, lungs, spleen, lymph nodes and peritoneum; tuberculous pericarditis; fibroid tuberculosis of lungs; fatty change in the liver; ascites; left hydrothorax; atelectasis of left lung; bilateral chronic adhesive pleurisy; undifferentiated carcinoma of left lung.

The microscopical study of the liver shows miliary and conglomerate tubercles some of which are of a rather large size. The large tubercles consist mostly of caseation enclosed by dense masses of fibrous tissue in which there is considerable leucocytic infiltration. The leucocytes consist chiefly of monocytes but many polymorphonuclear leucocytes are also present. Epithelioid cells are very few in number and only an occasional multinucleated giant cell is observed. In many places surrounding the large caseous areas, small miliary tubercles can be recognized. There is considerable atrophy of the cords of liver cells with degeneration and beginning fatty change in the central zones. Proliferating bile ducts in the fibrous tissue surrounding the caseous masses are numerous. The sections of the left lung show considerable thickening of the pleura and pulmonary framework. Extensive, poorly defined areas of caseation are scattered throughout the sections. Here there is considerable epithelioid cell proliferation and a few multinucleated giant cells. There are also many miliary tubercles.

A section through the grayish-white friable nodule found beneath the pleura of the left lower lobe shows a very different picture, there being a very cellular mass of tissue with the appearance of a well defined undifferentiated carcinoma. Numerous small atypical cells can be seen infiltrating the alveolar spaces and often filling them.

Typical tubercles of various sizes may be found in the spleen, adrenals, pericardium and peritoneum. Acid-fast microörganisms are found in acid-fast stains of the lesions in the spleen, liver and lungs; they have the morphology and appearance of tubercle bacilli.

## DISCUSSION

There has been much controversy as to the mode of infection in local tuberculosis of the liver. Felberbaum (4) is of the opinion that the infection reaches the liver by way of the portal circulation and is usually secondary to intestinal tuberculosis. However, three cases have been reported which were apparently primary in the liver. He states that the miliary tubercles have their origin in the hepatic capillaries of the portal system, through thrombosis in these structures and that these miliary tubercles often coalesce to form conglomerate tubercles or nodules which may later soften to form abscesses. Strauss, according to Pagel (9), in support of this theory has been able to produce positive results in animals on injection of portal blood from patients who died with intestinal

tuberculosis. However, Rosenkranz and Howard (10) are of the opinion that lesions formed in this way show no tendency to form abscess cavities or to enlarge by continuity or confluence. Kaufmann (6), Sheldon (11), and Morris (8) have emphasized the lymphatics as the probable conveyers of the infection from a tuberculous peritonitis to form tuberculous abscesses of the liver.

Whatever the mode of infection may be, nodular tuberculosis and tuberculous abscesses of the liver probably have a similar origin as is illustrated by Maximowitsch's (7) case in which there were multiple liver abscesses as well as large, firm, pseudoneoplastic nodules. Abscesses are probably the result of softening of the large tuberculous nodules. This case, however, showed no secondary softening or abscess formation.

Clinically, in local tuberculosis of the liver, there is usually enlargement of the liver without jaundice or pain. Fever is variable. There is usually a moderate leucocytosis with a predominance of polymorphonuclear leucocytes. However, there are no clinical phenomena which are characteristic.

The gross pathological diagnosis in the nodular type is quite difficult. The nodules are found raised from the surface of the liver as well as distributed throughout the liver substance. No umbilication of the surface is seen about the nodules. This may aid in the differentiation from neoplasms. The nodules appear as white, irregular masses of various sizes and shapes which are usually outlined by a thin fibrous capsule. They vary in size from a barely visible speck to 6 to 7 cm. in diameter. They are quite firm in consistency and on section have a grayish-white color. The picture closely simulates that of a metastatic carcinoma and seldom is the correct diagnosis made without the aid of the microscope. These nodules are not always confined to the liver but may be present in the spleen, lungs, lymph nodes and peritoneal surfaces as in the case reported here.

Histologically the condition is easily diagnosed as an infectious granuloma, but the demonstration of the acid-fast bacilli in the tissues is at times very difficult. There are but few giant cells present and the round cell and epithelioid reactions are strikingly diminished about the large necrotic areas. Frequently small typical tubercles may be found surrounding the large caseous nodules, and in these the acid-fast microorganisms are more numerous, as was found in our case.

It is interesting to speculate on the relationship of the tuberculosis

to the undifferentiated carcinomatous nodule found in the lung. It has long been known that tuberculosis is quite common in debilitated carcinoma patients; but it is difficult to attribute this relationship in this case.

SUMMARY

An unusual case of tuberculosis, in which the lesions are of the massive nodular type, is reported here. It is characterized by large, multiple, gray, firm nodules of various sizes and shapes distributed throughout the liver, spleen, lungs and lymph nodes. Grossly the lesions may be confused with a neoplasm, but this is easily eliminated by the extensive masses of caseous necrosis and the demonstration of acid-fast bacilli.

The presence of the undifferentiated carcinoma of the lung in this case presents the problem of the relationship of malignancy to tuberculosis.

REFERENCES

(1) ARIEL, M. B.: Virchow's Arch. f. path. Anat., 1930, *279*, 137.
(2) ROLLESTON, H. D.: Diseases of liver, gallbladder and bile ducts, ed. 2, London.
(3) DECRESPIGNY, C. T., AND CLELAND, J. B.: Med. Jour. Australia, May 5, 1923, *1*.
(4) FELBERBAUM, D.: New York Med. Jour., 1912, *96*, 481.
(5) GOYLE, A. N., VASUDEVAN, A., AND KRISHNASWAMY, K. G.: Indian Med. Gaz., 1934, *69*, 72.
(6) KAUFMANN, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin & Leipzig, W. de Gruyten & Co., vol. *1*, 1922, p. 731.
(7) MAXIMOWITSCH, A. S.: Zentralbl. f. Chir., 1927, *54*, 2292.
(8) MORRIS, E.: Amer. Rev. Tuberc., 1930, *22*, 585.
(9) PAGEL: Quoted by ROSENKRANZ AND HOWARD (10).
(10) ROSENKRANZ, K., AND HOWARD, L. D.: Arch. Path., 1936, *22*, 743.
(11) SHELDON, W. P. H.: Lancet, 1927, *2*, 1343.
(12) WALKER, A. G.: U. S. Vet. Bur. Med. Bull., 1930, *6*, 196.

# Lawrason Brown

## 1871–1937

Lawrason Brown died at his home in Saranac Lake on Sunday, December 26, 1937; his last words typical of his life, for he had sought above all things the truth in medicine, yet never missed an opportunity to soften a trying moment for a patient or a friend. When his medical friends, called by his first sudden attack late Christmas Eve, had sought to soften the news to him, he asked, "What's the matter with you fellows? Don't you know or are you afraid to tell me?" And then told them what they had refrained from telling him. When they came again early that Sunday morning he smiled and said, "What did I tell you? Merry Christmas!"—and was gone.

Lawrason Brown was born in Baltimore, Maryland, September 29, 1871, the son of William Judson and Mary Louise (Lawrason) Brown. He attended Baltimore City College and the Johns Hopkins University, graduating from the latter with honors in 1895; the quality of his work being further attested by his election to Phi Beta Kappa. He entered the Johns Hopkins Medical School where his ability and personality soon attracted the regard of his teachers, notably that of Doctor Osler and Doctor Welch; which regard ripened in the after years into warm personal friendships.

While in his third year of Medical School, he developed tuberculosis and was sent to Saranac Lake where he came under the care and influence of Doctor Trudeau. His friends little dreamed that he, like Doctor Trudeau, would live to translate his personal misfortune into a life of lasting benefit to mankind, and to place his name among those of the few great leaders who have inspired and guided the successful campaign for the control of tuberculosis. After a year he returned to Johns Hopkins where he received his M.D. in 1900, and then went back to Saranac Lake to take charge of Trudeau (then the Adirondack Cottage) Sanatorium.

In 1914 he married Miss Martha Louise Harris of Baltimore, and her complete understanding of and sympathy with that inner fire which kept him tirelessly at work gave him a support without which his remarkable accomplishments would hardly have been possible.

Lawrason Brown
1871–1937

He was an indefatigable worker and throughout his life gave freely of his time and energy to further the cause of medicine, often at a cost to himself known only to those nearest to him. His magnificent courage was such that, even when a baffling skin malady was robbing him of his sleep and making it impossible over long periods for him even to wear a shoe, he would appear at important meetings, when a lesser spirit would have been at home and in bed, and, passing off with a smile and a jest any reference to himself, would give his full attention to the matter in hand. His life was undoubtedly shortened by this course, but to him life was of little importance compared to the opportunity it gave for adding to the understanding of the baffling problems of tuberculosis.

He was one of the founders of the National Tuberculosis Association, serving on its Executive Committee and as its President in 1922. He founded the American Sanatorium Association and was its President from 1919 to 1923. He took an especial interest in the American Climatological Association, of which he was a member for thirty-four years and President in 1920, and, with the late Dr. Gordon Wilson, was largely responsible for its expansion into the American Clinical and Climatological Association. He was a member of the Association of American Physicians, the American Association for Thoracic Surgery, the American Association for the Advancement of Science, the American Public Health Association, the American Medical Association, the Medical Library Association, the New York Academy of Medicine, and a Fellow of the American College of Physicians.

He served on many boards, among others those of the Trudeau Sanatorium, the New York State Hospital at Ray Brook, the Waverly Hills Sanatorium at Louisville, the Potts Memorial at Livingston, New York, the Henry Phipps Institute of Philadelphia, and The Milbank Foundation. He was a member of the committee appointed by the Surgeon General for the evaluation of the Framingham demonstration, and in 1934 was appointed by Governor Lehman to the New York State Board of Social Welfare.

He served during the World War as consultant in tuberculosis, spending some time at Camp Devens in that capacity, and was a member of the American Legion.

In the midst of his widespread national activities he always found time for the affairs of the Trudeau Sanatorium and the village of Saranac Lake. He was a leader in the founding of the Saranac Lake Tuberculosis Society, having a large part in raising the funds for its support, and, as

was his wont, giving liberally of his own means; he was the active chairman of its Relief Fund and of its Occupational Therapy Committee. He organized the Stevenson Society for the purchase and preservation of the cottage occupied by Robert Louis Stevenson and was the first President of the Stevenson Club of America. He was on the staff of the Reception Hospital and of the Saranac Lake Hospital, a trustee of the Saranac Lake Free Library, a member of the Saranac Lake Board of Trade and he took a lively interest in the schools and school children. He helped organize the Adirondack Good Roads Association and was a member of the Association for the Protection of the Adirondacks. He founded the Osler Club for the study of medical history, which hobby he shared with his old teacher and friend for whom the Club was named.

His work at Trudeau Sanatorium was in itself sufficient to satisfy the desires of any ordinary man; and, had he done nothing else, he would still have made his name honored as a leader in the tuberculosis field. When he took over the residency of the Sanatorium in 1900 there was none of the organized medical routine which has made that institution a standard for the sanatorium world. For years, every moment he could spare from the regular care of the patients was given to perfecting its organization as a centre where thorough medical care, keen clinical observation and scientific research combined not only to give its patients the best possible chance of recovery, but also to make its results and its records available as a guide for the new institutions then being established in all parts of the country. He inaugurated its system of accurate medical records, and also that for the follow-up studies of its discharged cases and in these records he searched constantly for all facts there recorded which would add to the understanding of tuberculosis. In the twelve years he was active head of the Sanatorium he published forty articles based upon these studies.

This work of collecting and making available to the world the wealth of information found in these medical histories was perhaps Lawrason Brown's greatest contribution to the welfare of mankind, for, in addition to helping to a clearer understanding of tuberculosis, he changed our whole conception of a sanatorium from that of a mere home where patients lived in the open air to that of a well organized centre where patients are given the highest type of medical and social aid, and where, through constant stimulation of its staff to clinical and laboratory research, the quality of this service is undergoing continual improvement. The best was never quite good enough to his mind, and he inspired the same feeling in all who worked under him.

But, in his passion for scientific medicine, he never for a moment lost sight of the patient as an individual. In the Sanatorium, as in his private work, he seemed always to have time for their personal problems; always planning to lessen the burden of the long inactivity of the cure. In 1904 he published the Journal of the Out-Door Life using it as a vehicle for instruction to the patients and at the same time for awakening them to outside interests. He edited it, paying the yearly deficits himself, until it was taken over by the National Tuberculosis Association in 1910. He interested the patients in botany and in the study of birds, and in 1905 started an open-air shop where crafts and bookbinding were taught. He was largely instrumental in the establishment of the Medical Building where new admissions are thoroughly studied; the Medical Library; the research and X-ray laboratories where he worked in close coöperation with Petroff and Sampson; the Ludington Memorial Infirmary and the Training School for Nurses. He took great interest in the Trudeau School of Tuberculosis, and was never more himself than when surrounded by a group of younger men, asking and answering questions; his mind alert for the opportunity to fire their imagination and to awaken in them enthusiasm for that eternal search for the truth which was such a compelling force in his own life. He loved a good argument, and it was not uncommon, especially with younger men, to hear him take a position quite different from what he really believed just to see how clearly he could induce them to think out what he believed the true answer. He loved the society of younger men and had few equals in his power for bringing out the best in them.

When he left Trudeau in 1912 he continued on its visiting staff, making regular visits until 1929 when ill health forced him to stop. He continued his active interest in its affairs up to the time of his death, always delighting in advising and consulting with Doctor Heise, whose work and friendship he valued deeply.

His contributions to medical literature brought him international recognition as one of the outstanding authorities on the diagnosis, treatment and control of tuberculosis. His *Rules for Recovery from Tuberculosis* has guided more patients in their cure than any other book. *Intestinal Tuberculosis* (with H. L. Sampson) and *The Lung and Tuberculosis* (with Fred H. Heise) are the two outstanding studies of his work at Trudeau. He was a contributor to Osler and McCrae's *Modern Medicine*, Klebs' *Tuberculosis*, Tice's *Practice of Medicine*, Cecil's *Textbook of Medicine* and Blumer's *Therapeusis of Internal Diseases*, and since 1922 he had edited the department of Diseases of the Chest in the

*Year Book of General Medicine.* In addition to all of this his miscellaneous publications were nearly one hundred and fifty in number. At the time of his death he was busily engaged with a book on the History of Tuberculosis and had completed all but the last two chapters. His interest in the publications of others was as keen as though they were his own. Nothing could have been more characteristic of the man than his action on learning that Dr. William Snow Miller had no fund available for the publication of his book on the anatomy of the lung. He immediately started a subscription to raise the needed funds, writing personally to men in all parts of the country. He could have secured the entire amount from any one of several sources but, in spite of the extra demand upon his own too limited time, preferred to give Doctor Miller the gratification of knowing that the gift represented the widespread appreciation in which he and his work were held.

Among other honors which came to him were the degrees of Doctor of Science from Dartmouth in 1931 and the Medical College of Virginia in 1936. Two other American universities sought to confer degrees upon him but his failing health made it impossible for him to be present to accept them. In 1933 the National Tuberculosis Association awarded him the Trudeau Medal in recognition of his studies in tuberculosis.

He was a member of the Phi Kappa Psi, Phi Beta Kappa and Alpha Tau Omega fraternities, and of the Charaka Club and the Grolier and Century Clubs of New York.

His interests extended far afield from his life work of medicine. Medical history was his pet hobby but he was widely read in general literature, and old books, prints, wood-cuts, paintings, birds, flowers, bookbinding, golf and athletics in general (he was a famous athlete in his college days), civics and politics all had their appeal to his enquiring mind, giving him a ready footing of mutual interest with people of all classes. This, combined with his high professional ability, his cheery smile, his sympathy, his optimism and the example of his own courageous life, made him beloved as a physician beyond the lot of most men.

Simple and unspoiled by the honors which came to him; forgetting his own severe physical disabilities in his efforts to alleviate those of others; inspiring with his rare courage and his insatiable thirst for the truth; charitable to all save to himself; with an interest in his fellow man which took no heed of high or low, of rich or poor, of race or creed; "with forward face and unreluctant soul" he lived his life.

D. R. L.

## NOTE

Due to the very recent revival of interest in extrapleural pneumothorax attention is directed to what appears to be the first detailed report on a large series of patients. Olivier Monod (1) discusses in a well illustrated paper the technique, indications and the maintenance of extrapleural pneumothorax, based on observations on 40 patients in the Laennec Hospital in Paris.

The older literature on this procedure, which is not as new as recent discussions would indicate, is summarized by Alexander (2). In the period between Alexander's summary and Monod's paper a number of case reports (3) have appeared.


(1) MONOD, O.: Technique, indications et entretien du pneumothorax extrapleural, Ann. méd.-chir., 1938, *3*, 1.

(2) ALEXANDER, J.: The collapse therapy of pulmonary tuberculosis, Charles C. Thomas, Springfield, Illinois, 1937, p. 403.

(3) DUFOURT, A. P., SANTY, AND BÉRARD, M.: À propos du pneumothorax extrapleural, Rev. d. l. tuberc., 1937, *3*, 446.

HAUTEFEUILLE, E., AND DREYFUS-LE FOYER: Le pneumothorax extrapleural thérapeutique, Presse méd., 1937, *1*, 859; Rev. d. l. tuberc., 1937, *3*, 436.

NISSEN, R.: Die chirurgische Behandlung der Oberlappenkaverne, Schweiz. med. Wchnschr., 1937, *67*, 334.

# A FUNCTIONAL TEST IN CHRONIC PULMONARY DISEASE[1,2,3]

BENJAMIN H. SCHLOMOVITZ, A. B. THOMPSON AND L. GRANT GLICKMAN

A method that can be used in clinical work to estimate respiratory efficiency and therefore disability in silicotic pulmonary fibrosis is presented in this paper.

Many laborers exposed for years to the inhalation of certain dusts, composed of or associated with silica, eventually develop acute or chronic pneumonoconiosis which is characterized by a generalized pulmonary fibrosis. Roentgenologically this fibrosis (excluding those produced by asbestos and granite) has been rather universally classified into three groups or stages, called either first, second and third or early, moderate and advanced infiltration. The extensive literature on pneumonoconiosis has been presented by Davis and Salmonsen (1), Gardner (2), and others.

In assessing respiratory disability in this industrial disease, the majority of clinical observers deny such disability in uncomplicated first-stage silicotics, and admit its presence in third-stage silicotics whether or not complicated by infection or cardiovascular disease. However, in estimating disability in second-stage silicotics, considerable difference of opinion has arisen in interpretation of the signs and symptoms. No relatively simple method of determining the efficiency of the respiratory apparatus is available as yet, and the age group of these silicotics corresponds to the decades when cardiovascular disturbances are prone to appear as concurrent complicating factors. Therefore, adequate medical supervision, particularly of second-stage silicotics, depends on the discovery of objective criteria of respiratory efficiency (McCann (3), Moncrief (4)) and the proper evaluation of the pulmonary changes which may occur as a result of cardiovascular pathology.

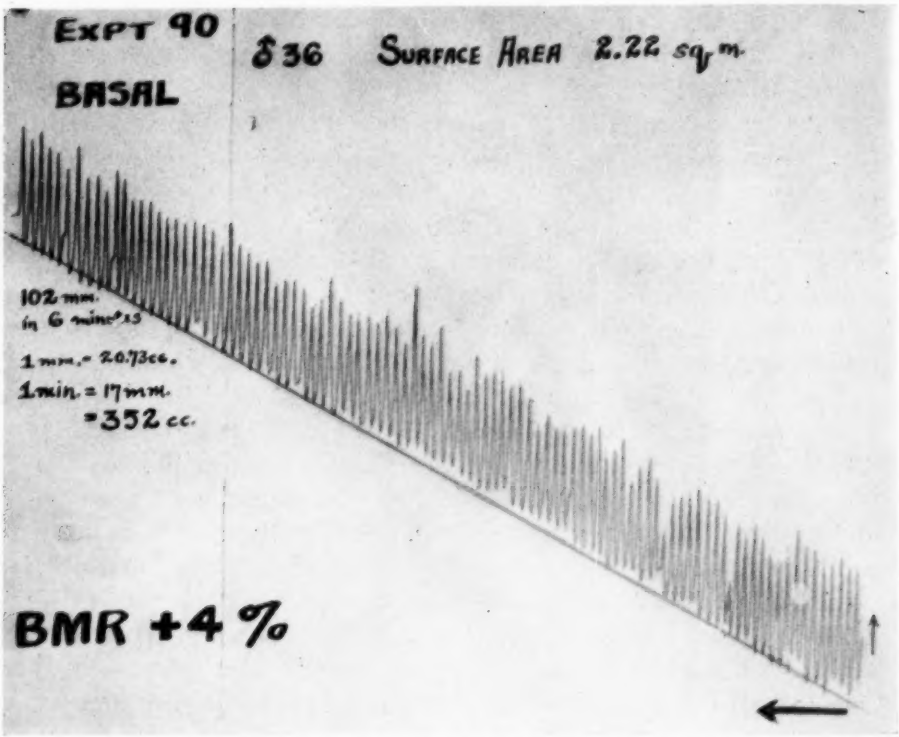
[1] From the Veterans Administration Hospital, Milwaukee, Wisconsin.

[2] Published with the permission of the Medical Director of the Veterans Administration, who is not responsible for opinions expressed or conclusions drawn by the authors.

[3] A preliminary paper was presented before the American Physiological Society, April, 1935. See Abstracts of the meeting.

METHOD

We sought a solution of this problem by studying the respiratory reaction of silicotic individuals to an exercise test, more particularly the variations in oxygen usage as disclosed by the increased oxygen demand after a standardized form of physical activity. Hill (5) in 1922 stated that "the only practicable means of following the recovery process in




Read all tracings from right to left. Each mm. is equivalent to 20.73 cc. of oxygen

FIG. 1. Tracing of basal metabolic rate, which was plus 4 per cent, or 17 mm. (352 cc.) per minute.

man is that of determining the oxygen intake following exercise," and Evans (6) noted that it would be well if data "could be confirmed by observations with some closed-circuit apparatus." Such a method was adopted by us (figures 1 & 2). The oxygen consumption during the recovery phase following moderate muscular activity was registered graphically, and the excess oxygen usage recorded.

On three to five separate days, individuals were exercised after a

twelve-hour postabsorptive resting period. Some were investigated in the nonbasal state. The exercise was done for 45 to 60 seconds and comprised the shoulder-to-floor carriage (about five feet) of a ten-pound dumb-bell grasped in each hand for 25 times, or roughly 5,000 ft. lbs.

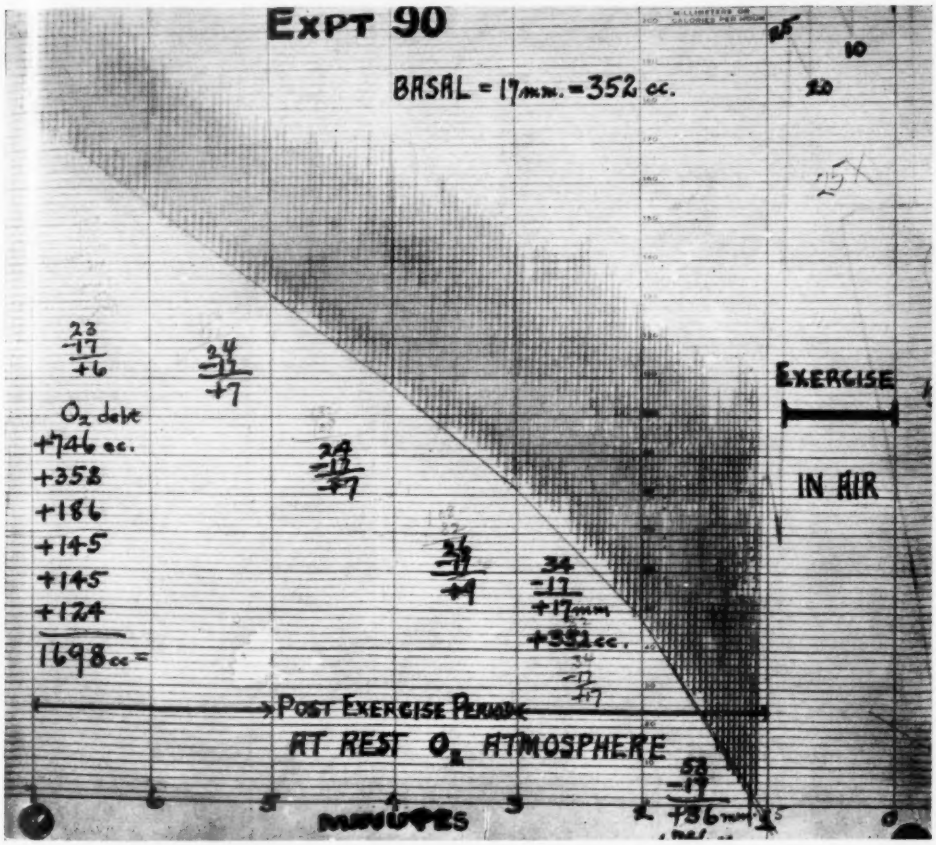



FIG. 2. Response to the exercise test by same subject. Period of exercise in air is shown in first minute; then subject in prone position is connected with the metabolism recording apparatus, and the response in the following 6 minutes (1 to 7) is shown. The excess oxygen usage for the 6 minutes is 1,698 cc., or 765 cc. per square metre of body surface.

(675 kilogram metres), bearing in mind the fact that movement of the body masses involved (mainly head, trunk, arms) forms a part of the energy demand. In some instances five to fifteen seconds elapse after exercise before the tracing is started. In the next successive seconds care must be observed in making the proper reading because of the

greatly increased ventilatory efforts. The exercise is performed in atmospheric air. Then postexercise determinations are made with the subject breathing into an ordinary basal metabolism recording apparatus containing practically pure oxygen except for the nitrogen from the first exhalations after the subject is connected with the apparatus. For this part of the test no corrections need be made for temperature, humidity, or barometric pressure.

Such increased oxygen demands following physical activity were studied in (*1*) healthy individuals, those having (*2*) thyroid dysfunction, (*3*) tachycardia, (*4*) cardiovascular disease, and (*5*) emphysema, as well as those having (*6*) silicosis.

That the dumb-bell test, as employed in this study, was not an exacting one was further confirmed by a special group of experiments in which the cost of work in terms of oxygen consumption for the 5,000 ft. lbs. (675 kilogram metres) was determined (to be reported in detail elsewhere). Briefly, these cost experiments showed that the average excess oxygen usage *during the one minute of exercise* was 1,175 cc., or about 4 times the basal metabolic rate. The average mean variation was 6.3 per cent. For the seven minutes, the average total oxygen cost, or requirement, was 1,090 to 1,445 cc. per square metre of body surface.

The 5,000 ft. lb. exercise was used as the standard because it certainly is not permissible to exact work from individuals, even for one minute, that would involve overload responses or excess strain.

The oxygen cost of the exercise adopted by us falls within the range of *moderate* exercise such as cited by Schneider (7), Hill (8), Lowsley (9), Kahn (10), Bainbridge (11), Simonson (12), Hanson (13), and many others. It does not even approach the possible maximum oxygen intake of about 4,000 cc. during one minute of excessive or severe exercise as determined by Hill and others. Sir Thomas Lewis (14) states that "healthy young adults, untrained to the work, will lift the 20 lb. bells 40 to 60 times in double the number of seconds before approaching the full effort." See also Henderson and Haggard (15).

Some investigators have sought a practical application of the determination of oxygen debt in cardiac cases (16) and in pulmonary tuberculosis (17). None of them, except Katz (16) and his fellow workers or Eyster (16), made actual and total minute-to-minute observations starting immediately at cessation of the muscular activity. Cases predominantly pulmonary, with or without cardiac impairment, have apparently not been reported before. Besides our April, 1935 communi-

cation before the American Physiological Society, a preliminary report on only a few advanced silicosis cases was presented by Jacobaeus, Nylin and Almberg in the fall of 1935 (18).

## DATA

Table 1 gives a summary of the groups studied, the number of subjects in each group of cases, the excess oxygen consumption per square metre

TABLE 1

*Summary by groups giving range (extremes), average and exceptions for 6 minute postexercise oxygen usage per square metre of body surface*

| GROUP | CASES IN A GROUP | | RANGE IN CC. | AVERAGE | EXCEPTIONS | FACTOR OF INCREASE: EXCESS OXYGEN DIVIDED BY BASAL RATE |
|---|---|---|---|---|---|---|
| Healthy subjects | 14 | Normal pulse response (a) | 688– 806 | | | 4.1–5.7 |
| | 5 | Fast pulse response (b) | 676– 823 | 750 | 904 | 3.9–5.9 |
| | 3 | Ambulatory cases (c) | 607– 772 | 678 | | 2.6–3.9 |
| | 3 | Lindhard effect (d) | 904–1,115 | | 904–1,115 | |
| Thyroid dysfunction | 7 | (e) | 651– 734 | | | 2.9–6.8 |
| Emphysema | 5 | Uncomplicated | 355– 549 | 457 | | 2.2–3.5 |
| Silicotics | 5 | 1st or early stage | 705– 883 | | 574; 587 | 3.7–5.5 |
| | 8 | 2nd or moderately advanced | 371– 618 | 500 | 697 | 2.1–5.0 |
| | 3 | 3rd or far advanced | 609– 707 | 663 | | 3.7–4.6 |
| Cardiacs | 3 | No pulmonary fibrosis (f) | 1,014–1,182 | 1,079 | | 6.9–8.2 |
| | 3 | With emphysema | 738–1,094 | 869 | | 4.4–6.7 |
| | 3 | With silicosis (g) | 723– 736 | 729 | | 4.1–4.6 |

(a) pulse returns to normal two minutes after exercise
(b) pulse persisting at 100 or above two minutes after exercise
(c) no previous basal test required; had breakfast
(d) subject held breath during exercise, found only in healthy cases
(e) hyper- or hypoactivity of thyroid glands, shown by BMR
(f) no pulmonary changes in X-ray films
(g) second-stage silicosis plus organic cardiac changes

of body surface for six minutes following exercise, and the factor of increase over the individual basal metabolic rate in each case. In preliminary calculations, inspection of the factor of increase in oxygen consumption and the values for excess oxygen per square metre of body surface showed that the factor of increase was not as reliable an index as a

basis of comparison with data that might be derived in other investigations. This was first evident from an analysis of the ambulatory cases (c). Just as height and weight play the most important rôles in determining basal metabolism, so do these same factors affect the final oxygen value in exercise. An intensive statistical analysis is not indicated because of the small numbers in each series. The variations, however, are significant, because the cases were selected with care. It must be appreciated that silicotic individuals have a great tendency to become tuberculous. These were eliminated and later verified as such by post-

TABLE 2

*Normals*

| EXPERIMENT NUMBER | AGE | WEIGHT | HEIGHT | S SURFACE IN SQ. METRES | BMR | BASAL $O_2$-USAGE PER MIN., UNCORRECTED | EXCESS $O_2$-USAGE AFTER EXERCISE: CC. IN SUCCESSIVE MINUTES | | | | | | T TOTAL CC. FOR 6 MIN. | T + S = CC. PER SQ. METRE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1 | 2 | 3 | 4 | 5 | 6 | | |
| | | *lbs.* | *in.* | | | | | | | | | | | |
| 5 | 44 | 146 | 71½ | 1.84 | +12 | 300 | 612 | 321 | 321 | 73 | 73 | 73 | 1,472 | 800 |
| 8 | 39 | 143 | 66¾ | 1.73 | −0.2 | 263 | 628 | 245 | 122 | 110 | 110 | 110 | 1,322 | 765 |
| 18 | 35 | 138½ | 66½ | 1.70 | −0.2 | 255 | 678 | 346 | 160 | 25 | 25 | 25 | 1,258 | 740 |
| 48 | 36 | 239 | 65¼ | 2.14 | +3.9 | 356 | 929 | 390 | 224 | 58 | 58 | 68 | 1,727 | 806 |
| 80 | 18 | 154 | 69½ | 1.85 | +4 | 321 | 653 | 342 | 176 | 52 | 52 | 31 | 1,306 | 705 |
| 84 | 21 | 130 | 66¾ | 1.67 | −6 | 249 | 477 | 269 | 269 | 145 | 124 | 62 | 1,347 | 806 |
| 75 | 46 | 171 | 65¼ | 1.84 | −4 | 263 | 566 | 338 | 151 | 110 | 131 | 131 | 1,426 | 775 |
| 78 | 43 | 166½ | 73 | 1.97 | −3 | 276 | 574 | 346 | 243 | 263 | 77 | 77 | 1,578 | 800 |
| 90 | 36 | 213 | 74 | 2.22 | +4 | 352 | 746 | 352 | 187 | 145 | 145 | 124 | 1,700 | 765 |
| 92 | 38 | 119½ | 63¾ | 1.55 | −9 | 218 | 466 | 259 | 114 | 83 | 104 | 52 | 1,078 | 694 |
| Average..... | 35½ | | | 1.85 | | 284 | 632 | 317 | 195 | 106 | 89 | 75 | 1,414 | 765 |
| Extremes..... | 21 | | | 1.55 | | 218 | 466 | 245 | 114 | 25 | 25 | 25 | 1,078 | 694 |
| | 46 | | | 2.22 | | 356 | 929 | 390 | 321 | 263 | 145 | 131 | 1,727 | 806 |

mortem examination. Constancy in reaction was tested by making three or four separate determinations in some of the cases.

To avoid further repetition in the text all figures for excess oxygen usage represent *cc. per square metre of body surface* during the six minutes following the exercise.

Fourteen healthy individuals with adequate pulse reaction, return to preëxercise level within two minutes after exercise, were found to be in the range 688 to 806 cc. (see table 2 for examples) and five with persistent high pulse-rates after exercise had values from 676 to 823 cc. Inspection

of the last column in table 2 shows that for the 6 minutes the excess oxygen usage averaged 765 cc., with a maximum variation of 9 per cent. Comparisons on the basis of square metre of surface area have been found to be most significant as is evident in the last column of table 2. Ambulatory healthy subjects who had eaten breakfast ranged from 607 to 772 cc. Seven cases with either a high or low basal metabolic rate (thyroid dysfunction) had a range of 651 to 734 cc., and therefore were essentially normal. A few healthy subjects had high values, 904 to 1,115 cc. These held their breaths for some time during the exercise, and in this fashion showed what can be called a modified Lindhard effect (19). This never occurred in any other group.

Constancy in reaction on different days, regardless of activity, is shown in table 3.

TABLE 3

*Experiment 89. Oxygen usage after exercise*

| DATE | 1ST MINUTE | 2ND MINUTE | 3RD MINUTE | TOTAL |
|---|---|---|---|---|
| | *cc.* | *cc.* | *cc.* | |
| After basal | | | | |
| 3/11/35 | 621 | 310 | 124 | 1,057 |
| 3/12/35 | 688 | 315 | 128 | 1,131 |
| | 688 | 252 | 128 | 1,068 |
| Ambulatory | | | | |
| 3/13/35 | 746 | 248 | 82 | 1,077 |

Five emphysematous patients with no detectable cardiovascular disturbances yielded a decidedly low range, 355 to 549 cc., as compared to the healthy subjects.

All three patients with organic heart disease showed much higher than normal values, or 1,014 to 1,182 cc. As this reaction has been substantiated by other research (16) no further determinations were made by us. When the cardiac disorder was complicated by emphysema then the values tended to drop back to the normal range. For three such cases the values were 738, 869 and 1,094 cc.

The group of chronic silicotics showed a general tendency to drop below the range for healthy individuals; in this respect simulating the emphysematous cases. This was especially true in those with an uncomplicated second-stage silicosis, and here the values fell as low as 371 cc.; five out of eight cases ranged from 371 to 537 cc., while the remaining three cases were 608, 618 and 697 cc. respectively.

When a patient had a second-stage silicosis plus organic heart disease then the values reverted to the range of the healthy group. Three such cases gave figures from 723 to 736 cc. It has already been noted by others as well as ourselves that patients with organic heart disease have high values.

A number of pathologists believe that many patients with third-stage chronic silicosis develop cardiac impairment, and that may account for the fact that these cases did not have low values (609 to 707 cc.) but

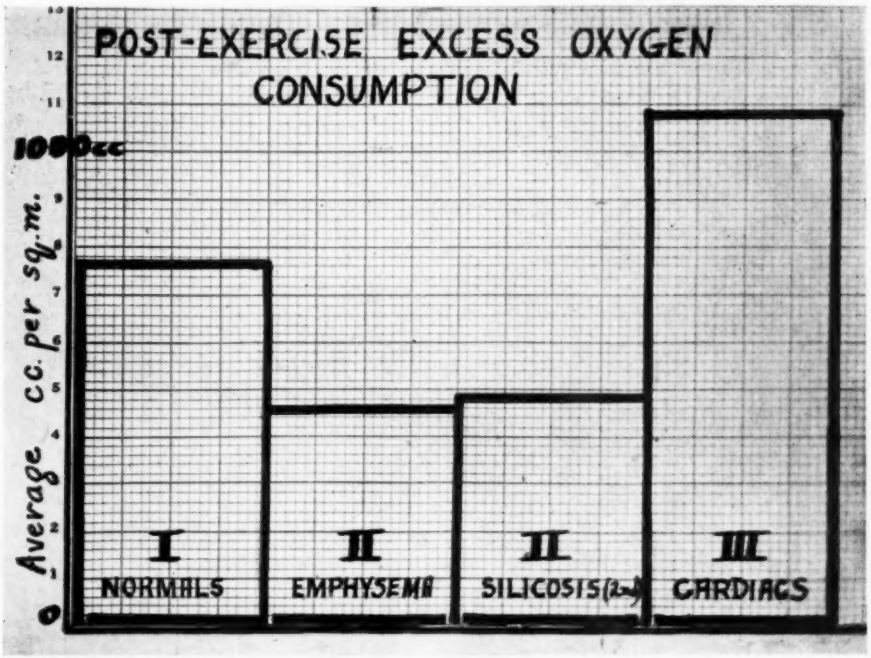



FIG. 3. See text for description

showed a tendency to come back to normal, apparently masking the effect of the silicotic fibrosis.

Although in this study we were not initially interested in the response of tuberculous individuals, opportunity to record the reaction of three apparently healed tuberculous cases, 30 to 70 years old, that had pulmonary fibrosis resembling first- and third-stage silicosis, disclosed a low or normal response.

Figure 3 graphically presents the essential differences in the various groups. The silicosis block shows the second-stage cases that gave low determinations.

## DISCUSSION

The experimental data show an interesting variation in the excess oxygen usage. This variation is apparently dependent upon some difference in each group of *uncomplicated* emphysematous, silicotic, and cardiac disease, as distinguished from normal or healthy individuals. Cases of emphysema or moderately advanced silicosis may have a decidedly low postexercise excess oxygen usage response as contrasted with cardiac cases. Healthy individuals and some of the second-stage silicotics are intermediate between these two series. It is interesting that many cases of second-stage silicotic fibrosis and pulmonary emphysema yield identical results in spite of the fact that the basic morbid changes of the two conditions are different. However, when both groups are complicated by organic heart disease associated with pulmonary congestion, then their original low reaction is obscured.

Several signs, hyperpnoea and reduced vital capacity, are characteristic of the three types: pulmonary fibrosis, emphysema, and pulmonary congestion. The postexercise response, however, evidently shows that functionally the intrapulmonary condition of many second-stage silicotics and emphysematous individuals is exactly opposed to what is found in cardiac cases. It is difficult to say wherein this difference arises. With the present state of our experimental knowledge concerning the other physiological effects of one minute's moderate exercise, further speculation seems fruitless (see review on dyspnoea by Tinsley R. Harrison (20) page 288). Our present aim was to record the changes that occurred. These changes are probably dependent upon alterations of residual air.

We believe that the dissimilar data in the noncardiac cases (emphysema or silicosis, second stage) and cardiac cases indicate a measure of pulmonary changes *per se*, and prove that this exercise test detects alterations in the pulmonary apparatus which can be measured; and that in spite of Lichtheim's (21) assumption there is not an extensive extrarespiratory epithelial tissue reserve from the functional standpoint. Many years ago Cloetta (22) and others had already demonstrated this fact by seeking its solution from other angles.

The phenomenon of sudden, rapid and marked increase in pulmonary ventilation, that occurs in healthy subjects at the instant of transition from rest to exercise before any physicochemical blood changes can occur, has been commented upon quite often. If the respiratory or breathing surface of the lungs were really adequate for demands in minor exercise or

if there were sufficient reserve of the respiratory epithelium at all times, such a critical event, early sudden increased ventilation, need not occur, according to some authors. On the basis of studies on man Himwich and Loebel (23) ventured the opinion that "the pulmonary mechanism may be a limiting factor in exercise," and Harrop and Heath (23) stated that "some functional obstruction exists in the lungs."

Can one conclude from these facts that we are reporting a method which distinguishes cardiac from pulmonary impairment?

To solve this problem proper value must be given to the data in which the oxygen response was uninfluenced by heart-rate in the normal cases or by thyroid dysfunction.

## SUMMARY

1. The postexercise excess oxygen absorption or oxygen usage of normal or healthy individuals subjected to moderate exercise is completed essentially within six minutes after the termination of the exercise, returning to the level of oxygen intake at rest.

2. A similar response is elicited in cases of thyroid dysfunction (hyper- or hypothyroidism), in cases with persistent tachycardia, and in normal individuals whose pulse-rates remain persistently rapid after exercise.

3. The excess oxygen used per square metre of body surface is comparable.

4. In silicosis, (*a*) first-stage cases generally give low normal responses or a little lower than normal response to the exercise test; (*b*) many second-stage cases show a diminished response, unless there is a complicating cardiovascular condition and then the responses rise to the normal range; and (*c*) third-stage cases usually give a normal or slightly below normal response.

5. Individuals with emphysema uniformly give a low response, unless they are complicated by cardiovascular disease, and then the values are normal or quite high.

6. Individuals with cardiovascular disease uncomplicated by pulmonary fibrosis respond to moderate exercise by a much higher value than the 6-minute postexercise excess oxygen usage of healthy subjects.

7. If lung lesions (silicotic fibrosis or emphysema) are present in patients with cardiovascular disease then the excess oxygen usage drops to the normal range.

8. An analysis of the above findings discloses the fact that uncomplicated cases of second-stage silicosis often give consistently an abnor-

mally low response to oxygen consumption after exercise. We believe that when this occurs it is an indication that this clinical respiratory test discloses the presence of a functional or physical disability, and that it is therefore an adequate efficiency test.

9. In clinical work, a preliminary basal oxygen consumption test need not be done, if the final calculation of excess oxygen usage is figured against surface area of the body.

## REFERENCES


(1) Davis, G. G., Salmonsen, Ella M., and Earylwine, J. L.: Pneumonokoniosis (silicosis) Bibliography, Industrial Medicine, Inc., Chicago, 1934; 1936.

(2) Gardner, L. U.: U. S. Pub. Health Bull. no. 187, 1929, (Appendix); Jour. Amer. Med. Assn., 1933, *101*, 594; Amer. Rev. Tuberc., 1934, *29*, 1.

(3) McCann, W. S., Hurtado, A., Kaltreider, N., and Fray, W. W.: The estimation of functional disability in the pulmonary fibroses, Jour. Amer. Med. Assn., 1934, *103*, 810.

(4) Moncrieff, A.: Tests for respiratory efficiency, Medical Research Council, Special Report Series, no. 198, 1934.

(5) Hill, A. V.: Mechanism of muscular contraction, Physiol. Rev., 1922, *11*, 310.
Lupton, H.: The recovery oxygen-usage after exercise in man, Jour. Physiol., 1922, *66*, 17.

(6) Evans, C. L.: Recent advances in physiology, P. Blakiston's Son & Co., Philadelphia, 1926, chap. xi.

(7) Schneider, E. C.: Physiology of muscular activity, W. B. Saunders Co., Philadelphia, 1933.

(8) Hill, A. V., and Lupton, H.: Muscular exercise, lactic acid, and the supply and utilization of oxygen, Quart. Jour. Med., 1923, *16*, 135.
Hill, A. V., Long, C. N. H., and Lupton, H.: Muscular exercise, lactic acid, and the supply and utilization of oxygen, Parts I–III, Proc. Roy. Soc., London, 1924, *96B*, 438; Part IV, 1925, *97B*, 96.
Hill, A. V.: Muscular movement in man, McGraw Hill Book Co., New York, 1927.
Hill, A. V.: Muscular activity, Williams & Wilkins Co., Baltimore, 1926.

(9) Lowsley, O. S.: The effects of various forms of exercise on systolic, diastolic, and pulse pressures and pulse rate, Amer. Jour. Physiol., 1911, *27*, 446.

(10) Kahn, M., Kahn, M. H., and Rosenbloom, J.: Functional diagnosis, Tice Practice of Medicine, W. F. Prior Co., Hagerstown, Maryland, 1927, ed. 2.

(11) Bainbridge, F. A.: Physiology of muscular exercise, Revision by A. V. Bock and D. B. Dill, Longmans, Green & Co., London, 1931.

(12) Simonson, E.: Handb. d. norm. u path. Physiol., *15*, 1930, pp. 577, 738.
Der Umsatz bei körperlicher Arbeit, Klin. Wchnschr., 1931, *10*, 1937.

(13) Hanson, E.: Handb. d. norm. u path. Physiol., 1931, p. 835; *18*, 1932, p. 319.

(14) Cotton, T. F., Rapport, D. L., and Lewis, T.: After effects of exercise on pulse rate and systolic blood pressure in cases of irritable heart, Heart, 1915, *6*, 269.

(15) Henderson, Y., and Haggard, H. W.: The maximum of human power and its fuel, Amer. Jour. Physiol., 1925, *72*, 264.

(16) Meakins, J., and Long, C. N. H.: Oxygen consumption, oxygen debt and lactic acid in circulatory failure, Jour. Clin. Invest., 1927, *4*, 273.

(16) BANSI, H., AND GROSCHURT, G.: Funktionsprüfung des Kreislaufs durch Messung der Herzarbeit, Klin. Wchnschr., 1930, *9*, 1902.

HERBST, R.: Der Gasstoffwecksel als Mass der körperlichen Leistungsfähigkeit, Deutsch. Arch. f. klin. Medizin, 1928, *162*, 33, 129, 257.

JAHN, D.: Sauerstoffverbrauch nach der körperlichen Arbeit, Klin. Wchnschr., 1930, *9*, 1757.

EPPINGER, H.: Handb. d. norm. u path. Physiol., 14, Sec. 2, 1931, p. 1289.

NYLIN, G.: Clinical tests of the function of the heart, Acta Med. Scandinav., 1933, Suppl. 52.

SOSKIN, KATZ, MARKEL, AND HENNER: The metabolic exercise tolerance test, Arch. Int. Med., 1934, *53*, 706.

EYSTER, J. A. E.: Personal communication.

(17) BLUHM, I. L.: Working test as clinical method for determining the function of the lungs, Acta Med. Scandinav., 1935, Suppl. 63–68.

(18) JACOBAEUS, NYLIN AND ALMBERG: Ibid., 1935, *86*, 455. Editorial on this preliminary report in the Lancet, 1936, *230*, 381.

(19) LINDHARD, J.: Untersuchungen über statische Muskelarbeit, Skand. Arch. Physiol., 1920, *11*, 145.

(20) HARRISON, T. R.: The pathogenesis of congestive heart failure, Medicine, 1935, *14*, 255.

(21) LICHTHEIM, L.: Die Störungen des Lungen-Kreislaufes, 1876.

(22) CLOETTA, M.: Über die Zirkulation in der Lunge und deren Beeinflussung durch Über- und Unterdruck; In welcher Respirationsphase ist die Lunge am besten durchblutet? Archiv. f. Exp. Path. u Pharm., 1911, *66*, 408; 1912, *70*, 409.

(23) HARROP, G. A., JR., AND HEATH, E. H.: Pulmonary gas diffusion in polycythemia vera, Jour. Clin. Invest., 1927, *4*, 53.

BOJE, O.: Über die Grösse der Lungendiffusion des Menschen während Ruhe und körperlicher Arbeit., Arbeitsphysiologie, 1933, *7*, 157.

HIMWICH, H. E., AND LOEBEL, R. O.: The oxygen saturation of hemoglobin in the arterial blood of exercising patients, Jour. Clin. Invest., 1928, *5*, 118.

# TUBERCULOSIS OF THE GUMS AND CHEEKS[1]

GEORGE G. MARTIN AND SHELDON W. KOEPF

Tuberculous ulceration of the mouth is an occasional complication of pulmonary tuberculosis. Rubin (1) gives an incidence of 1.44 per cent of oral involvement and states that other investigators have noted a similar incidence. In the last ten-year period, with 3,835 admissions to the tuberculosis serivice of the Buffalo City Hospital, five cases of involvement of the gums and cheeks have been found. This is an incidence of 0.26 per cent.

It is our purpose to report these five cases in detail because we have been unable to find a case series of tuberculosis of this particular area. Case series of tuberculosis of the tongue have been reported by Delevan (2), Finney (3), Handfield-Jones (4), and others. Rubin (1) in a discussion of tuberculosis as it occurs in various parts of the mouth states that involvement of this area usually occurs with multiple ulcerations in the mouth. When each of these cases was first examined, the oral lesions were confined to a single area and no concomitant lesions were noted. In one instance an extensive mouth lesion developed and in another two small secondary lesions, which healed in a few weeks, were observed. The type of lesion seen has been unusual because, with the exception of one case, the lesions have been deep seated rather than the more frequent superficial ulceration of oral tuberculosis. Three cases gave rise to a destruction of the antral floor and the development of a sinus into the antrum, which remained patent. Another case which showed an extensive indurated ulceration resembling malignancy was successfully treated. The oral lesion healed and an apparent arrest of the pulmonary tuberculosis occurred. These last two patients were of interest because their sputa were repeatedly negative. The repeatedly negative sputa did not rule out the possibility that at some time it did contain bacilli. The evidence in favor of this being a blood-borne infection rather than a direct inoculation is presented.

[1] From the School of Medicine and the School of Dentistry, University of Buffalo, and the Department of Medicine and the Department of Dentistry, Buffalo City Hospital, Buffalo, New York.

## CASE REPORTS

*Case 1:* C. F., file number 13169, age 21, was admitted on November 16, 1931. He was known to have tuberculosis since February, 1928. Upon admission he was confined to bed. Dyspnoea, a persistent cough and night sweats had been noticed since September, 1931. Examination revealed a chronic pulmonary tuberculosis, stage three, with bilateral infiltration throughout, as well as cavities in both apices. Sputa were repeatedly positive. For eight weeks some pain had been noted at the time of brushing the teeth but the patient denied bleeding, excessive salivation or discomfort, either with the mastication of food or while at rest.

An undermined ulcer was apparent in the left upper mucobuccal fold in the biscupid area. It was not indurated but was surrounded by a narrow zone of inflammation. Upon pressure, tenderness was elicited and a little purulent exudate was expressed. The lesion enlarged, and involved the area from the first bicuspid tooth back to the second molar region. The base of the ulcer appeared to be penetrating deeply and was dirty-white. By the use of a probe, the sinus was found to extend directly into the maxillary antrum, the opening being approximately 0.5 cm. in diameter. No teeth in the neighborhood showed caries or fillings. A few of the other teeth were slightly carious. The larynx showed marked oedema and ulceration, involving particularly the epiglottis and aryepiglottic fold. This was painful and caused distress upon swallowing. The remainder of the oral cavity was healthy. Although the submaxillary lymph nodes were somewhat enlarged, no other adenopathy was detected. The tonsils were small and slightly injected.

A biopsy showed typical tuberculous ulceration with giant and epithelioid cells and acid-fast bacilli.

The patient was too ill for extensive treatment, and no local treatment was given. When he died on March 3, 1932, the lesion had shown no tendency to healing. Autopsy was refused.

*Case 2:* J. G., file number 266827, age 24, was admitted March 28, 1932. His illness commenced in January, 1932, with a toothache in the upper right third molar area. Two teeth were extracted by a private dentist, following which the patient became seriously ill. A chest cold developed, with anorexia, weakness, a productive cough, and a 35 lb. loss of weight in four weeks.

Examination upon admission revealed a chronic pulmonary tuberculosis, stage three, with evidence of a small cavity in the left apex, and a bronchopneumonic type of infiltration throughout the left lung, a small cavity being apparent in the right side. Sputa were repeatedly positive.

The patient complained of soreness and difficulty upon mastication, dating from the time of extraction of the two teeth and localized to that area. Bleeding, excessive salivation and pain were denied. The upper jaw was edentulous,

the remaining teeth having been extracted in the interval prior to admission. The lower gums were receded and it was considered necessary to remove the remaining teeth. During the two weeks following admission extraction was performed with satisfactory healing. An ulcer was noted in the right molar area. This lesion was about 2.4 cm. in diameter, extending outward to the mucobuccal fold, and inward to the crest of the alveolar ridge. The edge was irregular, undermined and surrounded by inflammatory nodules. The base was covered with purulent exudate. No induration was present.

Until death occurred, on December 5, 1933, the mouth lesion was under observation. It showed no improvement at first, and extended more deeply. On August 19, 1932, a probe was passed through a perforation into the antrum of Highmore. Just before this the lesion had enlarged, and a secondary lesion had appeared over the third molar area on the lower jaw on the same side. This latter lesion presented an appearance similar to its precursor, and was about 1 cm. in diameter. Somewhat later a third ulcer formed over the lower third molar area of the opposite side.

Shortly after these lesions developed, a gradual improvement took place, and the secondary lesions healed. The original mouth lesion showed marked improvement with disappearance of active granulation tissue around the periphery. Although the opening into the antrum remained patent, the wall of the sinus appeared to be lined with healthy tissue. All symptoms referable to the mouth lesions disappeared.

In addition to the dental treatment outlined, the patient received galvanocautery to the unhealthy granulation tissue and ultraviolet radiation through a quartz applicator attached to a mercury-vapor-arc in a quartz lamp.

About seven months after admission, at the time the mouth lesion was showing its most rapid improvement, signs and symptoms of laryngeal involvement were noticed. Infiltration with ulceration developed and became extensive. There was destruction of the upper half of the epiglottis, with extension down into both true and false vocal cords. While the patient's general condition had previously shown improvement he became much weaker with the development of the laryngeal complication, and the lesion in the right lung showed definite signs of extension. In spite of all this, the oral lesion remained healthy.

A biopsy, taken on April 13, 1932, showed typical tuberculous granulation tissue, with characteristic tubercle formation, including giant cells. Acid-fast bacilli were found throughout the section.

Autopsy revealed that the right half of the hard palate was completely destroyed. Leading into the antrum was a large opening, the walls of which showed some unhealthy granulation tissue. Laryngeal findings were as described above. The pulmonary lesions consisted of multiple cavitations in both apices with widespread scattered areas of bronchopneumonia. Tu-

berculous ulceration involving the terminal ileum and the first part of the caecum was evident.

*Case 3:* J. D., file number 1095, age 51, admitted February 26, 1929, was a known case of tuberculosis since 1924. Six weeks before admittance, the patient developed a harsh productive cough, with associated loss of weight and night sweats. Examination revealed evidence of pulmonary tuberculosis, stage three, including coarse infiltration of both apices and cavitation of the left apex. In spite of considerable fibrosis, there were definite signs of activity in the left apex. The sputa were repeatedly positive, showing many bacilli on several smears.

Extensive dental caries, retained roots and gingivitis comprised the mouth findings; no tuberculous lesion was demonstrated at this time.

The patient was apparently improving, until October 24, 1931, when symptoms of tuberculous laryngitis developed. Increased weakness and activity of the chest lesion followed. Extraction of remaining teeth was completed by February 27, 1933, and healing occurred normally.

On April 27, 1933, the patient complained of soreness in his mouth. At the junction of the gum and the cheek in the region of the right maxillary molars, an ulcer with irregular and slightly undermined edges and a grayish-white base was found. Its diameter was 1 cm.; and surrounding the ulcer was a narrow, inflamed and elevated border. It seemed to be extending deeply, and tenderness was elicited, although pain and hypersalivation were denied. Gradually enlarging, the ulcer finally perforated the hard palate on July 15, 1933. This perforation, about 1 cm. in diameter, remained open, and assumed a more healthy appearance in response to treatment with galvanocautery, ultraviolet radiation, and a regimen of rigid oral hygiene.

In spite of the improvement of the oral lesion, both the chest and laryngeal conditions became more extensive until on December 23, 1933, death occurred. Biopsy had been refused; consent for autopsy was not granted.

*Case 4:* F. S., file number 15639, age 54, admitted August 26, 1930, gave a history of having had pulmonary disease at age of 16 years, and was a known case of tuberculosis in 1920. The history was that of severe cough, night sweats, and loss of weight during three months interval prior to admission. He appeared fairly well nourished and not acutely ill. Clinical and X-ray evidence of chronic pulmonary tuberculosis, stage three, with infiltration of both apices and cavitation of left apex, was demonstrated. The remainder of the chest showed fibrosis. Sputa were consistently negative.

He complained of soreness of the gums, with discomfort during mastication, although no pain or excessive salivation were noted. An area of granulation tissue, similar to that seen over a retained root, was found in the right upper

molar area. An X-ray film showed an area of alveolar absorption. No recent extractions had been done and the few remaining teeth, while not carious, showed septic gingivitis. When first seen the lesion was about 1 cm. in diameter, and was not a definite ulceration but appeared more like a granuloma. No secondary lesions were noted. Within a month the lesion was a clearly defined ulcer, and spread along the roof of the mouth. This ulcer was superficial with a grayish-white base, the edges appearing granular with many small elevations. These developed into typical tubercles, became necrotic and formed fresh ulcers. There was tenderness but no tendency to bleeding. The palate appeared, at first, to be spotted, and later, to be covered with unhealthy granulation tissue. The ulceration extended forward and outward over the buccal surface of the cheek, to involve the upper lip. A narrow zone of inflammation surrounded the ulceration. No induration was noted.

In spite of treatment with galvanocautery, radiation and dental care, the lesion progressed and became increasingly painful and troublesome. Sedatives were required and the diet was restricted to liquids.

The pulmonary lesion showed extension and definite evidence of activity, and, in addition, tuberculosis of the seminal vesicles and epididymis developed. He died on December 22, 1930.

Although this was the typical picture of tuberculosis, the biopsy was not definitely diagnostic. Circumscribed collections of cells, chiefly lymphocytes, were seen with considerable degeneration. The appearance was that of inflammatory granulation tissue. In spite of the concentric formation suggesting tubercle formation no acid-fast bacilli were found.

Autopsy verified the diagnosis of tuberculosis of lungs, prostate, seminal vesicles, epididymis, and mouth. The larynx was clear.

*Case 5:* F. G., file number 112905, age 51, was admitted November 4, 1935. The patient stated that he had lost twelve pounds in six months, but admitted no symptoms referable to the chest. He had worked in a foundry for 22 years, was undernourished and his muscle tone was only fair for a laborer. While clinical evidence of pulmonary fibrosis was apparent, the presence of an active pulmonary tuberculosis could not be demonstrated either at the time of admission or upon subsequent examination. Roentgenographic study of the chest showed a late second stage pulmonary fibrosis with a tendency to conglomeration in some areas (figure 1). In both apices were shadows suggestive of cavitation. Sputa were consistently negative.

The reason for seeking medical care was a swelling and stiffness of the left cheek, first noticed six months before and becoming progressively worse. Eating was difficult and the patient was forced to masticate on the right side although neither pain nor increased salivation were noted.

The left cheek appeared swollen and the left half of the upper lip was en-

larged to twice the size of the opposite side. The entire swollen area was dusky red. There was an area of necrosis on the vermilion border of the upper lip. Although it was impossible to open the mouth for a satisfactory examination of the buccal surface, an extensive lesion could be visualized involving the area from the upper lip backward and downward and covering the whole buccal surface from the alveolar ridge above to the mandible below. It extended backward to the first molar tooth. The lesion was hard and indurated, with a centrally situated ulcer about 2.5 cm. in diameter. The

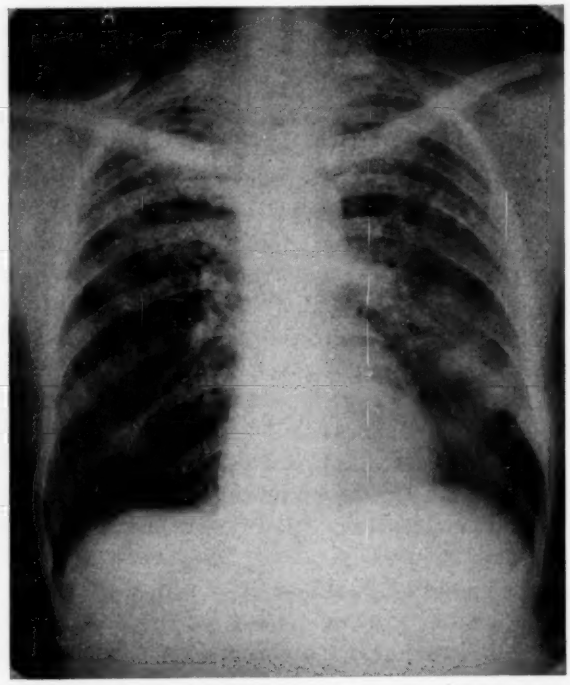


FIG. 1. Case 5. Extensive pulmonary fibrosis of occupational type with conglomeration in apices particularly evident on the right side.

territory surrounding the ulcer was inflamed, and in some areas there appeared a cauliflower-like proliferation. The ulcer was dark red in color, with a grayish exudate over the base. Fissuring was evident throughout. Tenderness was not elicited and the ulcer did not bleed easily. There was some enlargement of the submaxillary nodes on the involved side, but these were little larger than those of the opposite side. No other adenopathy was detected. The teeth were carious, with many retained roots. The remaining teeth, particularly those on the left, were abraded and had many sharp, knife-like edges. There was evidence of recent laceration of the left cheek. Because of

lack of several molars, the right side did not provide a good chewing surface. Many retained roots were abscessed and the gums were unhealthy, showing proliferation over the edges of the retained roots.

A provisional diagnosis of malignancy was made. Factors considered as modifying the picture included secondary inflammation from trauma and the oral infection.

A biopsy was taken and showed typical giant cells and in the area surrounding these, acid-fast bacilli in moderate numbers. There was distinct caseation and no evidence of malignancy. A diagnosis of tuberculosis was made.

The man was hospitalized and except for similar findings on a repeat X-ray taken December 10, 1935, no clinical evidence of tuberculosis was found. The sputa were consistently negative. Complete dental extraction was done, with subsequent satisfactory healing. Good oral hygiene and light therapy were instituted. The lesion showed prompt improvement. As the acute inflammation subsided, the characteristic appearance of the tubercles surrounding the ulceration became more evident. On June 10, 1936 there was no evidence of ulceration and a hard firm scar, covered with epithelium, remained. The man gained 22 lbs. in weight and his general condition was satisfactory. He has continued under observation, with no recurrence of the mouth lesion and no evidence of pulmonary activity.

## DISCUSSION

All five cases occurred in the male sex; this is consistent with the experience of other observers. Handfield-Jones (4) quotes case series showing the ratios of male to female varying from three to two, to twenty-three to one. This is of interest because it is well known that chronic ulcerative mouth lesions resembling tuberculosis occur more frequently in the male sex.

Consideration of the earlier dental hygiene of this group would seem to be of particular importance. The study of reported cases indicates that the relationship between inadequate dental hygiene and tuberculosis of the mouth has received little attention. It would appear that observers have attached little importance to poor dental hygiene as a predisposing or exciting cause for the development of this complication of pulmonary tuberculosis.

Moorehead and Dewey (5), discussing the mechanisms of defense of the mouth against invasion, stress the natural protection of the highly vascular mucous membrane, the antibactericidal action of the secretions and the possible action of the saprophytes. Theoretically, poor hygiene would interfere with the health of the membrane and reduce the effec-

tiveness of its defenses. An unhealthy condition of the oral mucous membrane and its gingival tissue is common in patients with tuberculosis. Experience, in our routine examination of patients admitted with tuberculosis, has shown a high incidence of gingival congestion and septic gingivitis. Similarly, Cipes (9) has noted the prevalence of poor oral hygiene in this type of patient. Factors which contribute to this are the debilitating disease, inability to properly carry out prophylactic measures and poor morale from a loss of interest.

In view of the frequency of an unhealthy mouth condition in patients with positive sputa, it is remarkable that oral tuberculosis does not occur more frequently. Rubin (1), in discussing this, further advances the possibility that when oral tuberculosis does occur, the circulatory route of invasion may be more frequent than direct inoculation. In two of our five cases, as previously stated, the sputa remained persistently negative though over thirty separate examinations were made in each case. They can be considered as presenting evidence in favor of blood-borne infection. It is realized that the sputa could have been positive prior to observation since an associated pulmonary tuberculosis was present.

Repeated trauma from the sharp knife-like edges of abraded and carious teeth was an important factor in the production of the lesion in case 5. The rapid improvement following dental extraction was evidence of this. It was obvious that the cheek had received repeated lacerations during mastication and on first thought it would appear that this was a case of direct implantation. The fact remains that a positive sputum was never obtained during an observation period of over a year.

The deep seated ulceration with destruction of bone noted in cases 1, 2 and 3 might be more readily explained by a blood-borne infection than by direct implantation. These three cases presented lesions which were clinically similar. They were characterized by a deep ulceration and necrosis of the bone. This resulted in a perforation through the floor of the antrum and development of a sinus which remained patent. The possibility of a tuberculoma or cold abscess from blood-borne infection is to be considered.

Another possibility to be considered is the extension of infection along the root canal of a carious tooth with a resultant tuberculous abscess in a situation similar to the common apical abscess. This possibility has been discussed by Moorehead and Dewey (5). It is probable that this portal of entry would result in the deep seated lesions noticed in the

first three cases. The absence of caries in the neighborhood of the lesion in case 1 indicates that this type of implantation, in this case, was not present. If extension through the root canal were important it would seem that children would be susceptible to deep seated bone lesions because the tooth is not completely formed and the root end is relatively patent. Nontuberculous abscesses are common and a tuberculous one should occasionally be reported. Such a lesion has never been recorded in the ward for tuberculous children at the Buffalo City Hospital.

The possible connection between dental extraction and tuberculosis requires consideration. It is common practice to perform the necessary extractions on patients with positive sputa. We have followed this practice and have seen no case in which there was an obvious relationship. Finney (3) and Rubin (1) state that such cases occur occasionally. In case 2 we have a history of an extraction three months before admission to the hospital. Pain had persisted and the patient stated that the lesion had never completely healed. It is possible that the tuberculous infection was present prior to the extraction. The patient became seriously ill following the extraction and had the mouth lesion at the time of admission. The extraction was done and early care given elsewhere, and definite information concerning the sequence of events was not obtainable. Apparently there was rapid extension of the pulmonary lesion following extraction. It was impossible to determine the anaesthetic used but it seems probable it was of the inhalation type. It is of interest that subsequent extraction of lower teeth was performed without delay in healing or apparent aggravation of the lung lesion. Local or block anaesthesia has been routinely used and it is the writers' impression that it is a safer anaesthetic for a patient with pulmonary tuberculosis in spite of the theoretical risk of direct implantation. The relationship between dental extraction and an extension of the pulmonary lesion appears to have been a close one in this patient (case 2). A similar relationship between tonsillectomy and an extension of the pulmonary lesion is better known. The type of anaesthesia used may be a determining factor in both instances.

If the deep seated lesions observed in cases 1, 2 and 3 were the result of implantation the area involved may be a factor in the development of this type of lesion. There is a definite tendency to retention of food particles in the postmalar pocket and there would be a similar retention of exudate in any lesion occurring here. This retention together with the trauma which occurs with chewing might lower the local resistance

and cause an extension to the deeper tissues. This area is closed off by muscle action when the mouth is open and adequate hygiene is always difficult.

Another possibility for the origin of these three lesions with extension into the antra would be within the nose. The course of the lesions seems to make this unlikely. There was no clinical evidence of nasal involvement in any of the five cases.

All patients had some discomfort particularly on taking seasoned food. Tenderness with chewing was noted at some stage in each instance. Case 5 complained of stiffness and inability to chew on the affected side. This was the result of induration rather than pain. In four cases no change to a soft or liquid diet was necessary because of discomfort with mastication. In case 4 the lesion spread rapidly and this patient required a soft or liquid diet after the lesion had extended beyond the gum and cheek. It would appear that pain is not a prominent symptom in tuberculosis of this area. Delevan (2) and Finney (3) conclude that pain may be present in the late stages, but that it is not an important early symptom. It would seem that pain is not more severe in tuberculosis than in carcinoma and that its value has been overstressed as a symptom in distinguishing between the two types of lesions. In no case was bleeding or excessive salivation noted. They are apparently more prominent symptoms when the ulceration involves the tongue.

Three distinct types of ulcerations were observed in the five cases. The first three cases presented a very similar appearance. They all occurred in the upper mucobuccal fold in the bicuspid and molar area. In one case two small secondary lesions with a similar appearance occurred on the gums of the lower jaw. The lesions of cases 1 and 2 remained single. These lesions were deep seated ulcerations which involved the bone, producing necrosis with perforation into the antra. In cases 2 and 3 this opening remained patent in spite of a tendency to healing with a healthy granulation tissue. Despite the depth of these ulcers and the very unhealthy appearing bases, there was little evidence of surrounding inflammation or induration.

These ulcers did not resemble the usual superficial ulcer of oral tuberculosis. The explanation for their occurrence in the region of the postmolar pocket may be in the relative immobility of this part of the mouth. Moorehead and Dewey (5), Rubin (1), Finney (3) and Handfield-Jones (4) discuss the importance of the mobility of the structures of the mouth as a factor in increasing the resistance to infection. This

mucobuccal area has not been described as a common site of oral tuberculosis. We have found no similar lesions in this area in other case series. In two of the first three cases a diagnostic biopsy was obtained and in the third case there was definite evidence of a pulmonary and laryngeal tuberculosis. There can be no doubt of the tuberculous aetiology of these cases. Finney (3) has reported a similar type of lesion which occurred in the lower jaw following dental extraction. This case was reported as case 14 of his series. These cases are of particular interest because it is a common impression that tuberculous ulceration is superficial and that this point is very useful in differential diagnosis.

Case 4 was a characteristic example of the superficial type of ulceration which is commonly described as being typical of oral tuberculosis. The condition spread widely by the formation of multiple new lesions around the periphery. This type of ulceration has been well described by Finney (3), Handfield-Jones (4) and others (1, 2, 8, 10).

Case 5 showed a third type of lesion which has previously been described, with detailed case reports by Wessely (6), Jeanselme, Lefèvre and Willemin (7). The lesion had the appearance of an advanced carcinoma of the cheek with a considerable amount of superimposed inflammation. The history and clinical examination of the chest showed some evidence of fibrosis but there was no reason to suspect a superimposed tuberculosis. The clinical impression concurred in by several examiners was that of a carcinoma of the buccal area aggravated by traumatism from the abraded teeth. The location on the buccal surface of the cheek is a common site for malignancy and the degree of induration was as great as seen in many carcinomata of this area. The neglected mouth and the age of the patient was in favor of this possibility. The absence of lymph node involvement was noted but was not considered of sufficient importance to modify the diagnosis. Biopsy revealed typical tubercle formation and acid-fast bacilli. The subsequent X-ray film showed some evidence of a pulmonary tuberculosis superimposed on an occupational pulmonary fibrosis. (See figure 1.)

In all five cases definite evidence of pulmonary tuberculosis was found and in four this was an advanced lesion. Without X-ray examination case 5 might have been suspected of being primary oral tuberculosis. It is of interest that this patient was one of the two with a persistently negative sputum.

An associated laryngeal tuberculosis occurred in the first three cases. There was no evidence of involvement of the tongue, tonsils or pharynx

in any of the five cases. There was no evidence of syphilis or leucoplakia. Lymph node involvement was not an important feature.

The histological picture of oral tuberculosis requires no elaboration. Our biopsies were definitely positive in cases 1, 2 and 5 with the finding of the typical histological picture and acid-fast bacilli. In case 4 the histological picture was suggestive but not definitely diagnostic. In case 3 biopsy was refused. In case 5 a biopsy report was the first clue as to the nature of the lesion. The difficulty in differentiating oral carcinoma and tuberculosis has been discussed by Feuerstein (8) who brings out the points usually considered in differential diagnosis. A study of the cases reported in the literature shows that many cases of oral tuberculosis have been diagnosed and treated as carcinoma prior to establishment of the correct diagnosis by the study of excised tissue. Feuerstein (8) has discussed the difficulty which arises when the pulmonary lesion is relatively silent as it was in case 5.

The five cases reported indicate that three distinct types of ulceration can occur in oral tuberculosis. A careful clinical and X-ray study of the chest and a study of the larynx is necessary to arrive at a correct diagnosis. The sputa may be negative and the clinical appearance of the ulceration is variable and not sufficiently characteristic to establish the diagnosis. A biopsy is always indicated and a search for the typical histological picture and acid-fast bacilli should be made.

General supportive measures and adequate treatment for the associated tuberculous lesions were used. Galvanocautery was helpful in destroying tuberculous granulation tissue. Indicated dental extraction and treatment were carried out in three cases with no untoward results. Light therapy including the use of local radiant heat and light and ultraviolet radiation was given and seemed to have a beneficial effect. It was particularly helpful in the indurated type of ulceration.

It is our impression that tuberculosis of this part of the oral cavity is a less serious complication of pulmonary tuberculosis than laryngeal involvement. It gives the patient less distress and gives less interference with nutrition. In cases 2 and 3 the lesions became quiescent in spite of advanced pulmonary lesion. In case 5 an apparent complete healing of the lesion occurred. In no case did the mouth lesion seriously alter the final outcome of the case.

## SUMMARY

1. Five cases of tuberculosis of the gums and cheeks are reported. All were complications of an associated pulmonary lesion.

2. Three cases show a deep seated ulceration involving the maxillary process and extending into the antrum. One case presented an extensive indurated lesion resembling a carcinoma. The other case was of the superficial type of ulceration usually noted in oral tuberculosis.

3. The mode of origin of these mouth lesions is discussed. The significance of the repeatedly negative sputum in two of the cases in connection with the blood-borne inoculation theory is noted.

4. The importance of associated dental lesions in the development of oral tuberculosis is discussed. It is suggested that more consideration be given the problem.

5. The infrequency of pain is noted.

6. Three of the cases occurred in the mucobuccal fold. The importance of the area and the unusual type of ulceration are pointed out.

7. Tuberculosis of the gums and cheeks is a less serious complication of pulmonary tuberculosis than laryngeal involvement.

## REFERENCES

(1) Rubin, E. H.: Amer. Rev. Tuberc., 1927, *16*, 39.
(2) Delevan, D. B.: New York Med. Jour., 1887, *45*, 536.
(3) Finney, J. M. T., and Finney, J. M. T., Jr.: Surg., Gyn. & Obstet., 1925, *40*, 743.
(4) Handfield-Jones, R. M.: Lancet, 1923, *1*, 8.
(5) Moorehead, F. B., and Dewey, K. W.: Pathology of the mouth, W. B. Saunders, Philadelphia and London, 1925, pp. 192–203.
(6) Wessely, E.: Wien med. Wchnschr., 1928, *78*, 494.
(7) Jeanselme, Lefèvre and Willemin: Bull. Soc. Franç de derm. et de syph., 1927, *34*, 353.
(8) Feuerstein, B. L.: Amer. Jour. Surg., 1935, *29*, 313.
(9) Cipes, B. J.: Dental Cosmos, 1926, *68*, 50.
(10) Morrow, H., and Miller, H. C.: Jour. Amer. Med. Assn., 1924, *83*, 1483.

# THROMBOSIS OF PULMONARY ARTERY[1]

## A Clinicopathological Study of Six Cases

JAIME F. POU AND ROBERT CHARR

Antemortem thrombosis of the trunk or the main branches of the pulmonary artery is an unusual occurrence. According to Kampmeier (1) only 26 cases were reported up to 1934. Billings (2) saw 16 cases in 6,200 autopsies and Lubarsch (3) found 16 in 1,932 autopsies. Moeller (4) reported 51 cases of pulmonary artery occlusion. In most of them the occlusion was embolic and not thrombotic in origin and it occurred in small intrapulmonary arteries. From May, 1934 to May, 1937, 105 cases of pulmonary tuberculosis and 45 cases of anthracosilicosis came to necropsy at the White Haven Sanatorium. Among these were 6 cases of antemortem thrombosis of the pulmonary artery. The essential findings in these cases were as follows:

*Case 1:* No. 8426, male, aged 58 years, anthracite coal miner for 24 years, was admitted to the service of Dr. Martin J. Sokoloff on March 29, 1930. Chief complaint was dyspnoea for the last six months.

Physical examination: The chest was rounded. There was dulness over the upper lobe of each lung with bronchial breath-sounds. Scattered râles were heard over the bases. The heart sounds were distant.

His sputum contained tubercle bacilli.

On X-ray examination (figure 1) the upper half of each lung showed fibrotic consolidation with cavitation in the right upper lobe. The heart shadow was widened.

He was discharged after a year in fair health and was readmitted December 21, 1933, complaining of severe dyspnoea, cough and loss of weight. Physical findings were the same as on the previous admission. The sputum showed tubercle bacilli. Temperature and pulse were normal. Bed-rest relieved dyspnoea and cough. In July, 1934, dyspnoea returned with slight cyanosis and oedema of ankles. On August 15, 1934 these symptoms became worse, accompanied by pain in the epigastrium. Anasarca soon followed with severe dyspnoea and cyanosis. The cervical veins were engorged and pulsating. The heart sounds were distant and irregular with extrasystoles. Vene-

[1] From the Pathological Laboratory of the White Haven Sanatorium, White Haven, Pennsylvania.

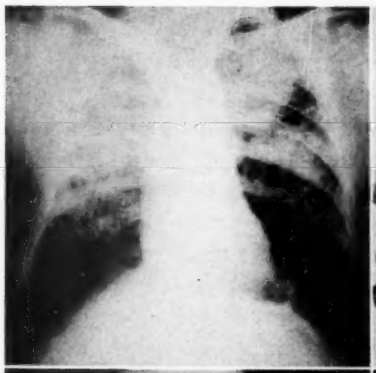


FIG. 1

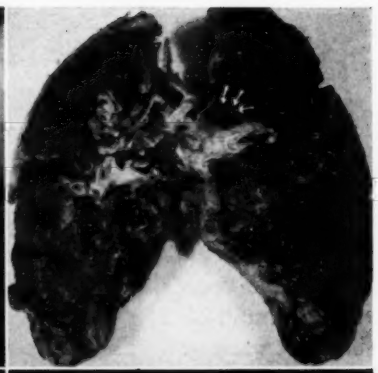


FIG. 2

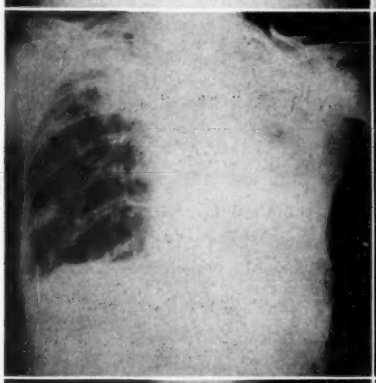


FIG. 3

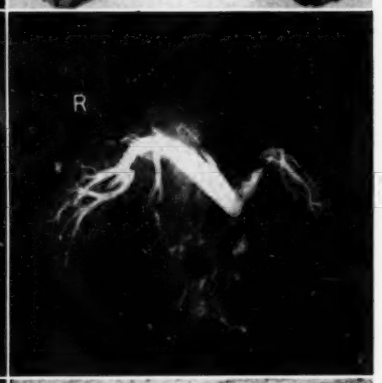



FIG. 4

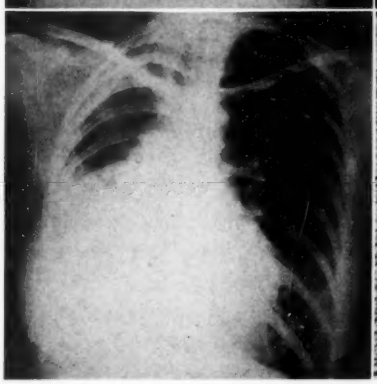


FIG. 5

FIG. 6

FIG. 1. Case 1. Fibrotic consolidation of upper half of each lung with cavity in right upper lobe. Widened heart shadow.

FIG. 2. Case 1. Arrows indicate the thrombus in the left pulmonary artery. The thrombus in the right pulmonary artery removed for study. Extensive anthracosilicosis. A tuberculous cavity in the right upper lobe.

FIG. 3. Case 2. Fibrosis of left lung with cavity in the upper lobe. Fibrosis of the right upper lobe with cavitation. Heart displaced toward the left.

FIG. 4. Case 2. Postmortem arteriogram of lungs. Note fibrosis of the left lung with marked vascular changes. Arrows indicate the thrombus in the left pulmonary artery.

FIG. 5. Case 3. Cavitation of the right lung with elevation of the diaphragm on that side. Emphysema of the left lung.

FIG. 6. Case 3. Cross section of wall of pulmonary artery showing: (A) fibrous strands invading the thrombus; (B) thickened intima; (C) media. × 100. Weigert's stain.

section was attempted but only 35 cc. of thick, dark blood could be obtained. The patient became very restless and apprehensive and died a few hours later.

Necropsy: The face was very cyanotic. The jugular veins were distended. The extremities were oedematous. The abdomen was distended with fluid and gas. The pericardial sac contained 250 cc. of straw colored fluid. The right auricle and ventricle were distended with blood; the myocardium was flabby. The trunk of the pulmonary artery was occluded by a pale, friable thrombus. It was firmly adherent to the intima and extended into the main branches of the pulmonary artery (figure 2). Both lungs showed extreme fibrosis due to anthracosilicosis with a cavity in the right upper lobe. The small arteries in the fibrotic areas were thrombosed. Two litres of clear fluid were found in the peritoneal cavity.

Microscopical findings: The pulmonary artery showed thickening of the intima with connective tissue proliferation and areas of fatty degeneration. The internal elastic lamina was reduplicated and fragmented. The thrombus was attached to the intima by platelets and fibrin. Extending into the thrombus were long strands of fibrous tissue. The smaller arteries showed marked sclerosis. The arteries near the cavity showed *endarteritis obliterans*. There were innumerable anthracosilicotic nodules and diffuse fibrosis.

*Case 2:* No. 7604, female, aged 62 years, was admitted to the service of Dr. Isadore Kaufman on March 2, 1937. Chief complaints were dyspnoea, pain in chest, cough, expectoration and loss of weight.

Physical examination: Lips and finger tips were cyanotic and ankles oedematous. The chest was rounded and the expansion was limited on the left. There were dulness and distant breath-sounds over the left lung. Scattered râles were heard over the bases. The apex beat was in the anterior axillary line; the heart sounds were regular but feeble. Blood-pressure was 90/70. The temperature varied between 97° and 99°F., the pulse rate between 99 and 118 and the respiratory rate between 24 and 38 per minute.

Sputum examination revealed tubercle bacilli.

On X-ray examination (figure 3) the left lung showed dense consolidation with cavitation. The right upper lobe was fibrotic and cavitated. The heart was displaced to the left.

On March 7, 1937 dyspnoea became worse, cyanosis of face deepened, the lips became purple, the cervical vessels were distended and pulsating. The patient was very restless and tossed abou. in bed complaining of boring substernal pain. At times she was disoriented. Her eyes were prominent. She died March 11, 1937.

Necropsy: Face, finger tips and toes were extremely cyanotic; the ankles were oedematous. The left ventricle was hypertrophied, the right ventricle and auricle were distended with blood. The myocardium was dark red and

fairly firm. The coronary vessels were thickened but patent. A thrombus was found in the left pulmonary artery a short distance above the bifurcation. It was firmly adherent to the intima, and completely occluded the left pulmonary artery (figure 4). The left lung was a mass of fibrosis from apex to base. There was a cavity in the upper lobe. The pulmonary tissue distal to the vascular occlusion was anaemic. All vessels were thickened. The right upper lobe was fibrotic and contained five small thick-walled cavities.

Microscopical findings: The pulmonary artery showed marked thickening of the intima by connective tissue. There were areas of fatty degeneration in the thickened intima. The internal elastic lamina showed a beady appearance due to localized areas of proliferation of elastic fibres. There was reduplication and fraying of the internal elastic lamina. The thrombus was attached to the vessel by fibrin and platelets. Extending into the thrombus were strands of fibrous tissue. The smaller arteries in both lungs showed marked sclerosis (figure 12) and some showed complete obliteration of the lumen. The right lung showed dilatation of the alveolar capillaries. All the vessels were engorged with blood. The coronary arteries were sclerotic without occlusion.

*Case 3:* No. 6020, female, aged 32 years, was admitted to the service of Dr. Charles Heiken on September 11, 1931. Chief complaints were cough, expectoration and loss of weight and strength.

Physical examination: There was dulness with roughened breath-sounds over the right upper lobe. A few râles were heard over the right apex. The heart was normal. The temperature was 99°F., pulse rate varied from 88 to 100, and the respiratory rate from 20 to 22 per minute.

Sputum examination showed tubercle bacilli.

On X-ray examination the right upper lobe was densely infiltrated with a cavity in the apex. The heart was normal.

Artificial pneumothorax was attempted on the right without success due to adhesions. In November, 1933 a phrenicoexairesis was done on the same side. The diaphragm became satisfactorily elevated but the cavity remained open (figure 5). On March 1, 1937 the patient complained of sharp pain in the right chest below the clavicle; her cough increased with difficult expectoration and her chest pain persisted. Soon dyspnoea set in. Slight cyanosis appeared on the lips. The patient became apprehensive. On March 21, 1937 dyspnoea became severe and cyanosis deepened. She tossed about in bed complaining of dyspnoea, pain in the chest and failing vision. At this time she developed definite exophthalmos and mental confusion. On the following day swelling of the face and ankles appeared. On March 27, 1937 dyspnoea, cyanosis and oedema increased and the patient thrashed about in bed. She died the same day.

Necropsy: The lips and the tip of the nose were deeply cyanosed, the eyes were prominent. The left ventricle was hypertrophied, the right auricle and ventricle were distended with blood. The myocardium was flabby. The coronary vessels were normal. The right pulmonary artery was completely occluded by a friable thrombus which was firmly adherent to the intima of the vessel. The right lung was almost entirely hollowed out by a large cavity. The remnants of the pulmonary tissue about the cavity showed marked anaemia. The right pulmonary artery ended in a blind pouch at the cavity wall. The left lung was emphysematous; its lower lobe was congested.

Microscopical findings: The pulmonary artery showed marked thickening of the intima (figure 6). The internal elastic lamina showed reduplication and fragmentation. The thrombus was adherent to the thickened intima. Extending into the thrombus was newly formed fibrous tissue, originating from the intima. Smaller arteries throughout the right lung showed tremendous thickening of the adventitia, many of them showed thickened intima and some complete obliteration of their lumina. All vessels in the left lung were engorged with blood. The myocardium showed fatty infiltration.

*Case 4:* No. 9790, male, aged 47 years, anthracite coal miner for 21 years, was admitted to the service of Dr. Frank A. Craig on January 26, 1932. Chief complaints were cough, expectoration and dyspnoea on exertion for a year.

Physical examination: The chest was rounded. There was resonance on both sides with loud breath-sounds. The heart was normal.

Sputum examination: No tubercle bacilli were demonstrated.

On X-ray examination nodular shadows suggesting anthracosilicosis of moderate degree were present in both lungs.

---

FIG. 7. Case 4. Fibrotic consolidation of the lower half of the right lung with cavitation. Dense infiltration in the middle third of the left lung.

FIG. 8. Case 4. Postmortem arteriogram of lungs. Note narrowing of vessels in hazy areas of fibrosis. Arrows indicate thrombus in the right pulmonary artery.

FIG. 9. Case 5. Fibrosis of the right lung with cavity in the upper lobe. Patches of fibrosis in left lung. Widened heart shadow.

FIG. 10. Case 5. Postmortem arteriogram of lungs. Note narrowing of vessels in right lung. Arrows indicate location of thrombus in the right pulmonary artery.

FIG. 11. Case 5. Arrows indicate thrombus in the right pulmonary artery. Extensive anthracosilicosis in both lungs. A tuberculous cavity in the right upper lobe.

FIG. 12. Case 2. Sclerotic intrapulmonary arteriole. Similar arterioles seen in all other cases. × 100. Weigert's stain.

FIG. 13. Case 6. Fibrotic consolidation of the upper half of each lung. Cavitation in the right apex. Emphysema of the lower lobes. Cardiac shadow slightly widened.

FIG. 14. Case 6. Postmortem arteriogram of lungs. Arrows indicate location of thrombus in right pulmonary artery. Note narrowing of vessels in the fibrotic upper lobe of each lung. Arteries in the right lower lobe are occluded as evidenced by failure of radiopaque substance to enter them.

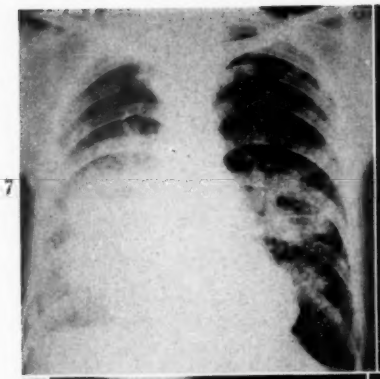


FIG. 7

FIG. 8

FIG. 9

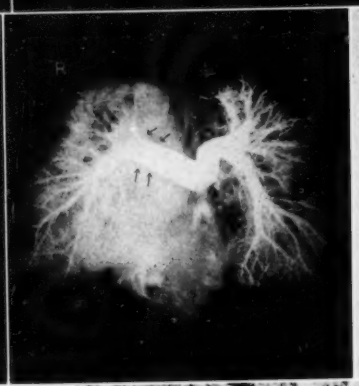


FIG. 10

FIG. 11

FIG. 12

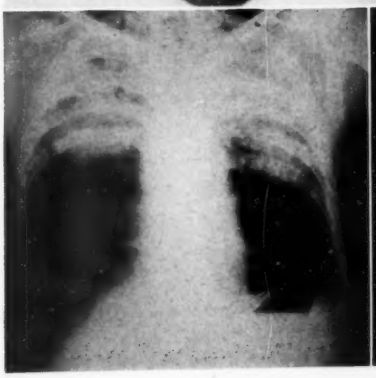


FIG. 13

FIG. 14

Temperature, pulse and respiratory rates were normal. A month later the patient left the Sanatorium.

On October 24, 1933 patient returned complaining of severe dyspnoea, cough, expectoration and loss of weight. Physical, laboratory and X-ray findings were the same as on the previous admission. In two months he left the Sanatorium in improved condition.

On November 18, 1936 he returned again with severe dyspnoea, cough, expectoration and loss of weight. Physical examination: There was dulness over the right chest with bronchial breath-sounds. The percussion note over the left lung was impaired and the breath-sounds were louder than normal. Scattered râles were heard over the bases. Blood-pressure was 114/78. X-ray examination (figure 7) showed consolidation of the lower half of the right lung and dense infiltration in the middle third of the left lung. There was a cavity in the right lung at the level of the seventh rib posteriorly and another one on the left at the level of the eighth intercostal space. Sputum contained tubercle bacilli. Temperature and pulse were normal; respiratory rate was 25 to 30 per minute.

For three months the patient improved in every way. Around the middle of February, 1937, he again complained of dyspnoea; soon cyanosis appeared. Severe pain in the epigastrium set in; this extended upward to the substernal region. The heart sounds were distant. On March 31, 1937 he became very dyspnoeic and intensely cyanotic. He sat up in bed complaining of pain and dyspnoea. Restlessness and apprehension were evident. Blood-pressure at this time was 102/88. Pulmonary circulation time was prolonged. Gradually the substernal pain became worse; dyspnoea and cyanosis became more marked. Slight oedema of the ankles appeared. Eight days after the onset of acute dyspnoea the patient died.

Necropsy: The lips were deeply cyanosed; the ankles showed slight oedema. The pericardial sac contained 150 cc. of clear fluid. Both ventricles were hypertrophied; the right auricle and ventricle were dilated. The myocardium was dark red and fairly firm. The coronary vessels were thickened but patent. A thrombus in the right pulmonary artery (figure 8) almost completely occluded the lumen. Detaching the thrombus revealed a roughened intima. The thrombus was firm and its cross section showed grayish streaks of fibrin and platelet deposits most dense at the site of its attachment to the intima. Lungs: The lower portion of the upper and middle lobes and the upper portion of the lower lobe of the right lung was a mass of anthracosilicotic consolidation. Within the centre of this mass was a tuberculous cavity. Throughout the remainder of the lung were numerous anthracosilicotic nodules intermingled with caseous tubercles. This lung appeared pale. The left lung was emphysematous. The posterior portion of the lower lobe was a mass of anthracosilicosis with a tuberculous cavity in its centre. Throughout

the remainder of the lung were anthracosilicotic nodules intermingled with caseous tubercles. The vessels in both lungs were thickened.

Microscopical findings: The pulmonary artery, where the thrombus was attached, showed thickening of the intima by connective tissue. The internal elastic lamina underlying the thickened intima showed fragmentation. In several places it was frayed out into thin strands. The intima was infiltrated by numerous small wandering cells and showed areas of fatty degeneration. The thrombus was attached to the thickened intima. Cross sections of the thrombus showed the usual coral-like laminae of platelets with marginal leucocytes and intervening red blood cells and fibrin. Smaller arteries throughout the lungs showed marked sclerosis. The sclerosis was most marked in the vessels located within the silicotic masses and in those adjacent to tuberculous cavities. Near the tuberculous cavities it was not uncommon to find the arteries completely obliterated. In some, the lumen of the vessels was reduced by thickeneing of the intima, in others by thrombosis. Practically all the vessels in both lungs showed marked thickening of the adventitia. Throughout the sections were numerous anthracosilicotic nodules with diffuse fibrosis of the pulmonary parenchyma. Intermingled with the anthracosilicotic nodules were caseous tubercles.

*Case 5:* No. 9863, male, aged 58 years, anthracite coal miner for 30 years, was admitted to the service of Dr. Charles Heiken on April 14, 1937. Chief complaints were dyspnoea, cyanosis, cough and expectoration. He had been well until a year previous to admission when he noted dyspnoea on exertion with cough and expectoration. Gradually the symptoms became worse. Shortly before admission dyspnoea became so marked that he had to go to bed. Soon cyanosis appeared.

Physical examination: The face was extremely cyanotic, the lips were dark purple. The eyes were prominent with congestion of the conjunctivae. The veins of the neck were full and slightly pulsating. The chest was rounded. Over the upper lobe there was dulness with bronchial breath-sounds. Crackling râles were heard at the bases. The apex beat was not palpable. The heart sounds were distant but regular and without murmurs. Blood-pressure was 80/70. There was no ankle oedema. The temperature was normal, pulse rate was 80 to 90, and respiratory rate 25 to 35 per minute.

The sputum contained tubercle bacilli. Blood count: Haemoglobin 106 per cent; R.B.C. 5,400,000; W.B.C. 8,200. Polymorphonuclear leucocytes 84 per cent, lymphocytes 16 per cent.

On X-ray examination (figure 9) the right lung showed fibrotic consolidation with a cavity in the upper lobe. The left lung showed scattered fibrotic areas throughout. The cardiac shadow was widened.

Following admission dyspnoea and cyanosis became worse. The patient

found it necessary to sit up in bed at all times. Although there was fulness of the cervical veins with some puffiness of the face, the ankles were not oedematous. Two weeks following admission, dull pain in the substernal region set in. Although there was no marked restlessness as in the other cases, the patient was apprehensive. On May 13, 1937 the patient died.

Necropsy: The face and finger tips were extremely cyanotic. There was no ankle oedema. The right auricle and ventricle were distended with blood. Both right and left ventricles were hypertrophied. The right pulmonary artery supplying the right upper lobe was thrombosed in its entirety; its terminal portion stopped at the border of the tuberculous cavity in the right upper lobe. There was much fibrosis in the upper and middle lobes principally due to anthracosilicosis. Scattered throughout the left lung were anthracosilicotic nodules with diffuse fibrosis of the lung. All blood vessels in both lungs appeared thickened.

Microscopical findings: The thrombosed pulmonary artery showed thickened intima due to connective tissue. The internal elastic lamina showed fragmentation. The thrombus was adherent to the intima by fibrin and platelets. Young fibroblasts had invaded the thrombus near its attachment to the vessel. Many of the smaller arteries showed marked sclerosis. Intermingled with the anthracosilicotic nodules were tubercles having fibrous capsules. The vessels in left lung were engorged. The myocardium showed fatty infiltration. The coronary vessels were thickened.

*Case 6:* No 9629, male, aged 60 years, anthracite coal miner for 35 years, was admitted to the service of Dr. Charles Aitken on October 14, 1933. Chief complaints were dyspnoea, moderate cough, expectoration and fatigue of eighteen months duration.

Physical examination: The chest was emphysematous. Over the upper two-thirds of both lungs was dulness with bronchial breath-sounds. The bases were hyperresonant. Crepitant râles were heard over the apices.

The sputum did not contain tubercle bacilli.

On X-ray examination the upper two-thirds of each lung showed fibrotic consolidation. The heart shadow was normal.

The patient was discharged, after five months, in an improved condition. On March 5, 1935 he returned with severe cyanosis, dyspnoea, cough and expectoration and loss of weight. Physical signs were the same as on the previous admission. X-ray examination revealed increase in the width of the cardiac shadow and fibrotic consolidation of the upper half of each lung with cavitation in the right apex (figure 13). The sputum did not reveal any tubercle bacilli. Temperature and pulse were normal; respiratory rate was 25 to 30. The pulmonary circulation time was prolonged. On May 29, 1937 marked dyspnoea appeared with pronounced cyanosis. The patient thrashed about in

bed. His vision became blurred. The lips were deeply cyanosed. He complained of substernal pain. Blood-pressure was 118/80. Haemoglobin 107 per cent; R.B.C. 5,800,000; W.B.C. 15,200 with a predominance of polymorphonuclear leucocytes.

Four days after the onset of acute symptoms substernal pain shifted to the right axillary region. His vision improved. Cyanosis and dyspnoea were still severe. The cervical veins were full though not pulsating. The ankles were not oedematous. The liver was not palpable. On the following day the patient died.

Necropsy: The lips and nose were cyanotic. There was no ankle oedema. The pericardial sac contained 50 cc. of clear fluid. Both ventricles were hypertrophied. The right auricle and ventricle were distended with blood. The myocardium was dark red and firm. Adherent to the posterior aspect of the right pulmonary artery was a pale friable thrombus, partly occluding the vessel lumen. Detaching the thrombus revealed a roughened intima. The terminal branches of the right pulmonary artery in the lower lobe showed emboli causing infarcts. The upper lobe of each lung showed much fibrosis due to anthracosilicosis. In the right apex were two cavities. Throughout both lungs were innumerable anthracosilicotic nodules. The right lower lobe showed infarcts. The vessels in the anthracosilicotic areas showed marked sclerosis (figure 14).

Microscopical findings: The thrombosed pulmonary artery showed intimal thickening by connective tissue. The internal elastic lamina showed fraying. The thrombus was invaded by fibroblasts from the intima. The intima and media were infiltrated with small wandering cells. The adventitia was thickened. The small arteries, arterioles and capillaries, especially in the right lung, showed marked sclerosis.

## DISCUSSION

The outstanding clinical features in these six cases of antemortem thrombosis of the pulmonary artery were rapidly increasing dyspnoea, cyanosis, engorgement of the cervical veins, pain in the chest or epigastrium, restlessness, mental confusion, exophthalmos, blurred vision, low pulse pressure with thin thready pulse and ankle oedema in the terminal stage of the disease. Because of the preëxisting pulmonary disease all the cases showed some dyspnoea and cyanosis on exertion. This was particularly true in cases 1, 4, 5 and 6 in which there were extensive anthracosilicosis and emphysema. However in all cases there was a time in the course of the disease when one had to look elsewhere for an explanation of the dramatic increase in the severity of the dyspnoea and cyanosis. Marked dyspnoea and cyanosis are uncommon in

ordinary pulmonary tuberculosis without effusion, pneumothorax, miliary or pneumonic spread of the disease. The manner in which cases 2 and 3, purely tuberculosis patients, manifested acute dyspnoea and extreme cyanosis was truly astounding. All the patients sat propped up in bed gasping for breath. At the same time they showed extreme cyanosis of the lips, nose and ear tips and nail beds. In all, the lips were deeply purple. The mucous membrane of the mouth as well as the conjunctivae was deeply injected; the cervical veins were full. The intensity of cyanosis in these patients was comparable to that of the *cardiacos negros* in Ayerza's disease. Kampmeier (1) and Montgomery (5) found cyanosis an important symptom in their cases.

Pain was a prominent symptom in all the patients. In cases 1 and 4 it began in the epigastric regions. Later it radiated upward into the substernal areas and remained there. In patients 3 and 6 pain was in the right chest and in cases 2 and 5 it was in the substernal areas. There was variation in the degree and location of pain in these patients, but the fact that it was present in all cases appears significant. Brenner (6) and Bogaert and Scherer (7) found chest pain in most of their patients.

In cases 2 and 3 the lungs with thrombotic pulmonary arteries had very little pulmonary tissue left. Practically the entire lung in both instances was hollowed out from the apex to the base. Yet the occlusion of the pulmonary arteries supplying these shell-like structures produced most acute dyspnoea, cyanosis and chest pain.

Restlessness and mental confusion were striking symptoms. All the patients except case 5 tossed about in bed as they gasped for breath. All of them showed some degree of transitory mental confusion. At times they were disoriented as to time and place. All of them were apprehensive and frequently talked of death. Mental confusion was probably due to cerebral ischaemia. Kampmeier (1), Billings (2) and Schramm (8) attached much significance to the mental symptoms in their patients.

In cases 2, 3 and 5 exophthalmos appeared as dyspnoea and cyanosis became very acute. In case 5 the conjunctival vessels were extremely engorged. Blurred vision was a marked symptom in cases 3, 4 and 6. Exophthalmos and blurred vision were probably due to oedema of the retrobulbar areolar tissues and passive congestion in the retina.

Oedema of the ankles was present in all patients except cases 5 and 6. It appeared in the terminal stages of the disease, indicating myocardial failure. Puffiness of the face was noted in cases 2, 3 and 5; it appeared

before the ankle oedema. Low pulse pressure was noted in patients 2, 4 and 5. Thin thready pulse was present in all patients.

We made no electrocardiographic studies. Bogaert and Scherer (7), McGinn and White (9) and Brenner (6) found prominent Q-waves in lead 1 and late inversion of the T-wave with a high origin in lead 3. In some, a tendency to right axis deviation was noted. McGinn and White (9) repeated the electrocardiographic studies after their patients had recovered and found the tracings to be normal in two of their nine cases. Extrasystoles, gallop rhythm and cardiac murmurs were observed by them. Extrasystoles were present in case 1. Bogaert and Scherer (7) pointed out the similarity existing between the electrocardiographic records of posterior coronary artery occlusion and those obtained in their patients with pulmonary artery thrombosis.

The X-ray examinations showed the character and extent of the pulmonary disease. In cases 1, 4, 5 and 6 the gradual increase in the width of the cardiac shadow was observed by Dr. John T. Farrell, Jr. The patients were too ill to be examined roentgenologically after the occurrence of the pulmonary artery thrombosis. Whether X-ray examination can aid in its detection is questionable. The postmortem X-ray examination of the chest failed to show the thrombus in these cases. The arteriograms of the lungs with the pulmonary arteries filled with radiopaque substance showed marked arteriosclerosis in the lobes which were most diseased (figures 4, 8, 10 & 14).

The physical findings of the lungs and heart were not helpful. Other than signs of chronic pulmonary disease and myocardial weakness at the terminal stages, the findings were negative.

The diagnosis of thrombosis of the pulmonary artery may be suggested by the clinical features already described. In a tuberculous patient without heart disease in the past, rapidly increasing symptoms and signs resembling acute myocardial decompensation should arouse suspicion of thrombosis of the pulmonary artery. Cardiac decompensation in ordinary pulmonary tuberculosis is not a usual occurrence. In coniophthisic patients with concomitant emphysema gradual decompensation of the right side of the heart is common. In such cases dyspnoea, cyanosis and oedema of the dependent parts may occur and thus simulate pulmonary artery thrombosis. However, extreme cyanosis, restlessness, exophthalmos and pain are uncommon.

A coronary artery occlusion may offer difficulty in differentiation. The onset in this condition is sudden except in the presence of chronic

myocarditis. Pain is more severe but dyspnoea and cyanosis are less marked than in pulmonary artery thrombosis. The curious pallor and profuse sweating commonly seen in coronary occlusion are absent in this condition. Spontaneous pneumothorax may be excluded by the physical signs. Intrathoracic malignant disease may be suggested. In this, the onset is more gradual. There is no restlessness. In pulmonary embolism the onset is sudden with marked pallor but usually slight cyanosis of the lips. Cold perspiration and violent vomiting often seen in embolism are lacking in thrombosis. Loss of consciousness is common in embolism but not seen in our cases. In nonobstructive embolism the symptoms may be milder, therefore, closely resembling thrombosis. Haemoptysis is very common in embolism but not observed in our cases.

To make a pathological differentiation between embolic and thrombotic pulmonary artery occlusion may present some difficulty. However, a careful study of the histological structure of the coagulum, its gross architecture in relation to the lumen and shape of the involved artery, the tenacity of its adherence to the intima and the apparent age of the clot in relation to the extent of atherosclerosis of the underlying intima may aid in establishing a correct differentiation. Furthermore, pulmonary artery embolism as a rule occurs as a complication to abdominal and pelvic operations or infections. Absence of thrombophlebitis in the veins of the abdomen, pelvis and the lower extremities and absence of antemortem thrombi in the right side of the heart are the points against embolism.

In our cases the manner in which the platelets, fibrin and other cellular elements of the blood settled on the atherosclerotic arteries suggested that the thrombi formed from the bottom up within those vessels. The invasion of the coagula by the strands of fibrous tissue originating from the thickened intima was another point in favor of primary thrombosis. In addition, the fact that the occlusion was limited only to those arteries whose terminal branches were located near the cavities or within the masses of anthracosilicotic consolidation indicated that this occlusion was the result of the condition of the pulmonary tissues surrounding them, and not due to accidental lodgment of incoming emboli from distant parts of the body. Had these vessels been occluded by emboli, it is difficult to conceive that the emboli would choose to lodge only in the vessels whose lumina were narrowed and tortuous. Moreover, in every case the occluding coagulum conformed exactly to the shape of

the involved vessel. In all the cases the clots could not be removed easily, so tenaciously were they adherent to the intima. In no case was there evidence of thrombophlebitis in the distant veins of the abdomen, pelvis or the lower extremities. In all cases the right auricles and ventricles were free from antemortem thrombi.

Various views have been advanced in regard to the pathogenesis of thrombosis of the pulmonary artery. Inflammation and degeneration of the artery (Bogaert and Scherer (7)), endarteritis (Boyd (10)), chemical changes in the blood due to destruction of the pulmonary tissues (Michelsson (11)) causing hyperinosis (Killian (12)) and an increase in the coagulability of the blood (Gragert and Wildegans (13)) are said to be aetiological factors. Increase in the blood calcium (Owre (14)), (Oehler (15)), polycythaemia, dehydration and anoxaemia may aid thrombosis. Myocardial insufficiency (Bauer (16)), (Dequervain (17)), (Rosenthal (18)) with consequent slowing of the pulmonary circulation (Michelsson (11)) plays an important rôle in thrombosis of the pulmonary artery. Bacterial infection (Karsner (19)) and invasion of the vessels by tumor cells may also aid in thrombosis.

In our six cases the extensive pathological changes in the lungs, marked atherosclerosis of the pulmonary artery and the gradual weakening of the right side of the heart were the principal aetiological factors. Cases 1, 4, 5 and 6 had wide-spread pulmonary fibrosis due to anthracosilicosis and tuberculosis. Cases 2 and 3 presented extensive cavitation of the lungs containing the thrombosed arteries. Atherosclerosis of the pulmonary artery is generally regarded as rare except in conditions such as mitral stenosis, emphysema, tuberculosis and chronic pleuritis.

In fifteen cases of anthracosilicosis associated with pulmonary tuberculosis and in thirteen cases of far advanced pulmonary tuberculosis which came to necropsy, the pulmonary arteries were injected with radiopaque substance and X-ray films made of them (20). The outstanding finding of this study was marked arteriosclerosis of the pulmonary vessels near the tuberculous cavities and in the areas of fibrosis, whether due to tuberculosis, anthracosilicosis or both. Frequently the small sclerotic vessels in these areas showed thrombosis. The arteriograms of cases 2, 4, 5 and 6 illustrate the above observation.

In every one of our cases the thrombosed artery was in the lung in which the pathological changes were more advanced. Tracing the thrombosed artery toward the periphery invariably showed that its terminal branches containing thrombi ended as blind pouches. These

terminal parts were located either at the centre of the anthracosilicotic consolidation or at the wall of a tuberculous cavity. The microscopical examination of the thrombosed arteries showed marked atherosclerosis.

It is true that injury to a vessel alone does not lead to thrombosis. Many pathologists maintain that in order for injury of vessel wall to lead to thrombosis there must also be slowing of the blood current. In all our patients there was evidence of myocardial weakness at some time during the course of illness. In cases 4 and 6 the pulmonary circulation time was prolonged. General passive hyperaemia in a vessel increases viscosity of that column of blood due to carbon dioxide accumulation. Increase in the viscosity of blood is another important factor in producing thrombosis. We feel that the atherosclerosis of vessels and stagnation of circulation in the diseased vessel, due partly to obstruction of its flow and partly to myocardial weakness, allowed settling of platelets and fibrin, thus forming a scaffolding for the deposit of other cells.

A bacterial infection might have had some influence in thrombosis in these cases. It is a known fact that the presence of bacteria in the neighborhood of a vessel produces inflammatory reactions of that vessel. In such instances thrombosis frequently occurs in the inflamed vessel. We pointed out that in our cases the terminal branches of the thrombosed vessels ended at the cavities containing mucopurulent material. The mucopurulent material in the cavities contained tubercle bacilli and pyogenic microörganisms. The products of these microörganisms might have caused inflammation of the nearby vessels thus paving the way for thrombosis. Lubarsch (21) in his study of thrombosis in man was able to exclude an infectious agent in only thirteen per cent of the cases.

## SUMMARY AND CONCLUSIONS

1. The clinicopathological findings of six cases of antemortem thrombosis of large branches of the pulmonary artery are described.

2. The outstanding clinical symptoms and signs of this condition were rapidly increasing dyspnoea and cyanosis, engorgement of the cervical veins, thoracic or epigastric pain, restlessness, mental confusion, exophthalmos, blurring of vision, low pulse pressure with thready pulse and slight oedema of the ankles in the terminal stages of the disease.

3. Differential diagnosis of thrombosis of the pulmonary artery from

myocardial insufficiency, coronary artery occlusion, spontaneous pneumothorax, intrathoracic new-growths and pulmonary embolism may be possible by a close observation of the clinical course of this condition.

4. Pathological differentiation of pulmonary artery thrombosis from embolism of that artery may be made by a study of the microscopical and macroscopical architecture of the coagulum, the tenacity of its adherence to the vessel, the age of the clot in relation to the atherosclerotic changes of the involved vessels, absence or presence of thrombophlebitis in the veins of the abdomen, pelvis or lower extremities and absence or presence of thrombi in the right chambers of the heart.

5. Extensive pathological changes in the lungs due to tuberculosis and anthracosilicosis, atherosclerosis of the pulmonary arteries and gradual myocardial weakening appeared to be the main aetiological factors in these cases.

6. Pulmonary artery thrombosis may be more common in chronic pulmonary diseases than generally believed.

The writers wish to express their indebtedness to Dr. Frank A. Craig and Dr. Joseph Walsh for their valuable suggestions and criticisms. The members of the Medical Staff were kind in allowing us to use the clinical notes on these patients.

## REFERENCES

(1) Kampmeier, P. H.: Jour. Thoracic Surg., 1934, *3*, 513.
(2) Billings, F. T.: Pennsylvania Med. Jour., 1921, *25*, 152.
(3) Lubarsch, O.: Quoted by Brenner (6).
(4) Moeller, P.: Ibid.
(5) Montgomery, G. L.: Jour. Path. & Bacter., 1935, *41*, 221.
(6) Brenner, O.: Arch. Int. Med., 1935, *56*, 1189.
(7) Bogaert, A., and Scherer, H. J.: Arch. du Mal. Couer, 1935, *28*, 714.
(8) Schramm, H. G.: Ztschr. f. Kreislaufsforsch, 1927, *19*, 713.
(9) McGinn, S., and White, P.: Jour. Amer. Med. Assn., 1935, *104*, 1473.
(10) Boyd, W.: The pathology of internal disease, Lea & Febiger Co., Phila., 1931.
(11) Michelsson, F.: Aerztliche Rundschau, 1929, *39*, 323.
(12) Killian: Quoted by Michelsson (11).
(13) Gragert and Wildegans: Ibid.
(14) Owre: Ibid.
(15) Oehler: Ibid.
(16) Bauer: Ibid.
(17) Dequervain: Ibid.
(18) Rosenthal, S. R.: Arch. Path., 1932, *14*, 215.
(19) Karsner, H. T.: Human pathology, J. B. Lippincott Co., Phila. and London, 1926.
(20) Charr, R.: Unpublished data.
(21) Lubarsch, O.: Quoted by Karsner (19).

# TUBERCULOSIS OF CERVICAL LYMPH NODES[1]

## The Incidence of Its Manifest, Latent and Obsolete Forms in Six Thousand Dispensary Patients

BRIAN C. THOMPSON[2]

One of the most noticeable features of the decrease in tuberculosis during the last thirty years has been the changed incidence of tuberculosis of lymph nodes. This type of the disease has become reduced throughout the civilized world and, although no comparable figures are available, it appears that this reduction has been much greater in some communities than in others. In the United States, for example, it is apparently approaching the vanishing point (1), whereas in certain districts of Great Britain (2) the proportion of tuberculous lymphadenitis to all forms of active tuberculosis reaches as high as 20 per cent. This disproportion is commonly attributed to the conspicuously purer milk supply of the former country, due to pasteurization and to elimination of infected herds, but, although the bovine tubercle bacillus has in the past been an important aetiological agent in this type of disease, there are many indications that it is not the only factor involved. The British figures quoted above were obtained in a district where the consumption of fresh milk is extremely small, averaging two-fifths of a pint per person per week (3). This is used almost entirely for cooking, and dried or canned milk, presumably sterile, is employed for infant feeding and similar purposes. Lymph node tuberculosis is still common among the Chinese, who drink little or no milk, and among Indians of certain reservations (4) who, in general, drink no milk at all.

Epidemiological evidence shows that the mortality from tuberculosis of all forms is falling, that the time of initial infection is becoming delayed (5), that metastatic types like miliary tuberculosis and bone disease are becoming rarer and that the adult type of pulmonary tuberculosis has a better prognosis. There is no evidence that tuberculosis of periph-

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Dorothy Temple Cross Research Fellow in Tuberculosis, Medical Research Council, Great Britain.

eral lymph nodes is decreasing any more rapidly than, for instance, tuberculosis of intrathoracic lymph nodes. In the case of the latter, it is probable that the infection, when it occurs, is prone to run a more benign course with a tendency to heal, owing in part to smaller dosage due to improved hygiene and control of the infective agents. It may well be that peripheral lymph nodes also receive a smaller dosage and that they may fail to show manifest disease, just as may be the case with the tracheobronchial nodes. In other words, the fact that tuberculous lymphadenitis is seen less frequently may be in part due to lessened severity, as well as to lessened incidence of infection.

The present survey was made in an attempt to determine the incidence of subclinical tuberculosis of the peripheral lymph nodes and of manifest tuberculous adenitis among patients of the Henry Phipps Institute, and the relationship between tuberculous adenitis and pulmonary tuberculosis.

## SOURCES OF THE PRESENT SURVEY

At the Henry Phipps Institute patients as a rule either present themselves on account of pulmonary symptoms or are referred for examination as contacts of known sufferers from tuberculosis. For this reason, lymph node tuberculosis is not commonly seen except as a complication of pulmonary disease.

The records were studied of 5,000 successive patients who paid their initial visits between March, 1933 and March, 1937. Routine examination of these patients included tuberculin tests and roentgenological examination. The latter was made by fluoroscopy with or without a subsequent film, films being taken in approximately half the cases. In many cases, especially those found to have pulmonary lesions, series of many films were taken. The following figures indicate the results of the X-ray examinations:

*Results of X-ray Examination of Chest*

| | |
|---|---|
| Number of patients X-rayed | 4,711 |
| Pulmonary tuberculosis, adult type | 941 |
| Pulmonary tuberculosis, childhood type | 507 |
| No thoracic tuberculosis (2 had abdominal tuberculosis) | 3,263 |

Pulmonary tuberculosis of the adult type was classified for convenience under three heads, as advocated by the National Tuberculosis Association (6):

*1:* Minimal; under this heading were included cases of latent apical infiltration, and pleurisy with effusion
*2:* Moderately advanced
*3:* Far advanced

Pulmonary tuberculosis of childhood type was classified under two heads:

*1:* Active, shown by enlarged tracheobronchial nodes with or without demonstrable parenchymal infiltration, in which calcification or other signs of healing had not been established. These lesions generally occurred below the age of 15, and usually below the age of 10 years.
*2:* Inactive, in which calcification was established and no active tuberculosis of lymph nodes or parenchyma was apparent. These lesions were found in both adults and children.

The figures were as follows:

| | | *Number* |
|---|---|---|
| Pulmonary Tuberculosis | | |
| Adult type | Minimal | 361 |
| | Moderately advanced | 251 |
| | Far advanced | 329 |
| Childhood type | Active | 58 |
| | Inactive | 449 |
| Total | | 1,448 |

The tuberculin test was made by intracutaneous injection of Purified Protein Derivative of Tuberculin (P.P.D.) in one or two strengths as indicated (7). In a certain number of cases the test was omitted for clinical reasons or was refused by the patient; in some cases the patient failed to return for the reading of the reaction. Of 284 patients who were not examined roentgenologically, 41 were positive and 164 negative. The latter were mostly very young children, in whom a negative tuberculin reaction presumably indicated freedom from infection, and in whom roentgenological examination was therefore regarded as unnecessary.

Of 3,263 patients in whom roentgenological examination showed no evidence of pulmonary tuberculosis, 2,746 were given a satisfactory tuberculin test. Two thousand two hundred and two (67.5 per cent) were positive and 544 (32.5 per cent) negative. It is realized that a negative tuberculin test is not absolute evidence of freedom from infection. The maximum dose used for these patients was 0.005 mgm. Purified Protein Derivative, which will almost always detect a tuber-

culous infection. It is noteworthy that, in the present series, 17 patients who showed roentgenological evidence of calcified lesions, presumably denoting healed tuberculosis in the lung and tracheobronchial nodes, were found to be negative to this dose of tuberculin. It is possible in these cases either that the degree of allergy was below the threshold of this dose but might have responded to a higher dose, or that the infection was truly obsolete and allergy no longer present. On the other hand, in some cases the roentgenological diagnosis may have been at fault, particularly in the 9 cases in which that diagnosis was based on fluoroscopy alone. In the 8 cases where X-ray films were taken, 6 showed evidence of calcification beyond any reasonable doubt. The remaining 2 are open to question, and in the light of the negative tuberculin reaction should perhaps be read as negative.

## ENLARGED CERVICAL LYMPH NODES

Of 5,000 patients examined in this series, 940 showed marked enlargement of cervical lymph nodes at the time of their first visit. Of these, 17 were judged clinically by prolonged observation, with or without histological confirmation, to be tuberculous. Of the remaining 923, one was found to be suffering from Hodgkin's disease and 6 from malignant disease secondary to new growths in the lung (five cases) or breast (one case). One other patient was acutely ill with scarlet fever.

There remained 916 patients with lymph nodes enlarged for reasons undetermined. The standard record sheet provides for a note on "cervical lymph nodes," which was utilized differently by the various clinicians responsible for the examination of patients. Enlargement of nodes was variously designated "palpable," "++," "moderate," "size of a lima bean," etc. It was found necessary to use considerable judgment in interpreting such observations in order to obtain approximately uniform results. Thus "palpable" cervical lymph nodes in a child would not be accepted as an abnormal feature, unless a special note implying abnormality had been added; and enlargement noted equally in cervical, axillary and inguinal or other groups, suggesting a "lymphatic diathesis," could also be ignored. In general it may be taken that the nodes included in this series were enlarged beyond normal limits but not to a massive degree, were not markedly adherent or fluctuant and had not broken down; and that they were situated in the upper part of the neck, probably in the upper deep-cervical (tonsillar) group. Enlarged supraclavicular or axillary nodes were not included under this head, because in cases where these were noted, there was either a definite aetiology,

septic, tuberculous or malignant, or there was generalized enlargement of all peripheral lymph nodes (lymphatic diathesis).

In many of these cases there was noted a condition of focal infection to which the lymph node enlargement might be attributed, such as enlarged or septic tonsils, dental caries or pediculosis. This information, however, was of little value in deciding whether the enlargement was merely secondary to local sepsis of this type, owing in part to the inconstancy of the observers and the absence of negative observations in cases without enlarged lymph nodes.

It is possible that in some of these cases the lymph node enlargement was due to tuberculosis. Tuberculous cervical nodes in a latent or healed stage may often escape diagnosis owing to their inconspicuousness or resemblance to the common minor hyperplasias. The writer has recently had opportunity of examining the protocols of 61 patients whose tonsils or adenoids, routinely removed at Johns Hopkins Hospital, Baltimore, were found to show histological tuberculosis.[3] Although in 57 of these the associated cervical lymph nodes were clinically noted as "enlarged," in only 24 were they diagnosed as tuberculous, 18 of them by biopsy. Of the remaining thirty-nine, 28 were examined after intervals averaging twenty years, by which time cervical lymph nodes were palpable in only fourteen cases. Gross manifestation of tuberculosis in these patients was thus exceptional.

If, as the writer believes, tubercle bacilli primarily invading the nasopharynx behave as they do when invading the lung, that is, producing a small retrogressive lesion at the site of entry and a more extensive lesion in the regional lymph nodes, then it is probable that many more cervical nodes are infected with tuberculosis than ever become clinically tuberculous. The lymph node which drains the tonsil (8) must reach a considerable size before becoming noticeable and X-ray examination may show extensive calcium deposits in a node in this situation which have never before attracted attention. It was felt that the present series might throw some light on the incidence of latent cervical node tuberculosis of this type, if the occurrence of lymph node enlargement could be correlated with positive tuberculin reactions in patients showing no roentgenological evidence of intrathoracic tuberculosis.

A total of 2,746 patients had negative roentgenograms and were given

[3] Through the courtesy of Dr. Samuel J. Crowe, Dr. James Bordley III, and Dr. John Baylor.

a satisfactory tuberculin test; lymph node enlargement (not suspected as being tuberculous or malignant) was noted in 443 (20.1 per cent) out of 2,202 tuberculin-positive patients, and in 151 (27.9 per cent) out of 544 tuberculin-negative patients. Thus the incidence of enlarged lymph nodes was actually slightly higher, though not significantly so, among tuberculin-negative than among tuberculin-positive patients, showing no evidence that latent tuberculosis of the cervical nodes was responsible for the positive tuberculin reaction in the latter group.

### CERVICAL LYMPH NODES CLINICALLY TUBERCULOUS

Clinically diagnosed tuberculous lymphadenitis occurred in 51 patients of the series. In 38 of these the lymph node lesions occurred prior to the patient's attending the Institute, and were healed or obsolete at this time in 34 patients, being diagnosed by the personal history, the records of some other clinic, or the presence of characteristic scars in the neck. In 5 of the 38 cases, X-ray examination showed calcified deposits at the site of the old lymph node lesion. In 8 cases nodes had been surgically excised, and in 28 there was a history of abscess-formation and chronic draining sinus. Of the remaining 2 cases, one showed marked calcification and the other had an active recurrence of the adenitis while under observation. It may be noted that, while X-ray shadows of calcification are presumptive evidence of old tuberculosis, the absence of such shadows does not mean that no tuberculosis has been present. Many tuberculous lymph nodes do not reach the stage of massive caseation and in them calcium may never be laid down. Even in nodes which have caseated and calcified, lime salts may be rapidly and completely resorbed. The writer has observed dense calcification in a cervical node which entirely disappeared within four months.

The distribution of previous tuberculous adenitis in this series was as follows:

*X-ray Diagnosis*

| | NO TUBERCULOSIS | CHILDHOOD TYPE INACTIVE | ADULT TYPE | | | TOTAL |
|---|---|---|---|---|---|---|
| | | | Minimal | Moderately advanced | Far advanced | |
| Number | 21 | 4 | 6 | 2 | 5 | 38 |
| Total cases in each group | 3,263 | 449 | 361 | 251 | 329 | |
| Percentage showing previous tuberculous adenitis | 0.64 | 0.85 | 1.66 | 0.80 | 1.50 | |
| | | | | 1.38 | | |

The incidence of previous tuberculous adenitis was thus more than twice as high among patients showing X-ray evidence of adult-type pulmonary tuberculosis as among patients in whom X-ray examination showed no evidence of tuberculosis (1.38 per cent as compared with 0.64 per cent). These two groups are directly comparable, as both came under clinic observation in the same way and both were subjected to the same routine investigation. The difference in incidence is therefore significant and indeed striking, since it is directly opposed to the view first expressed by Marfan in 1886 (9) and still widely held (10), namely, that lymph node tuberculosis tends to protect the individual from subsequently developing pulmonary tuberculosis. Though it was impossible from the material available to determine that no intrathoracic tuberculosis accompanied or preceded the original lymphadenitis in the above figures, there is strong presumption that in most cases the lymph node lesion appeared in advance of the adult-type pulmonary lesion.

## ACTIVE TUBERCULOUS ADENITIS

Seventeen patients had active tuberculous cervical adenitis at or about the time of their first visit: in 4 of these the disease was a recurrence of an old partially healed lymph node tuberculosis; in 6 cases there was associated pulmonary tuberculosis of adult type; in 3 cases, calcified tracheobronchial nodes; and in 2 cases, active, noncalcified tracheobronchial adenitis. The anatomical distribution was as follows:

*X-ray Diagnosis*

| ANATOMICAL GROUPS | NO TUBERCULOSIS | PULMONARY TUBERCULOSIS | | NOT X-RAYED | TOTAL |
|---|---|---|---|---|---|
| | | Adult type | Childhood type | | |
| Tonsillar | 4 | | | | 4 |
| Submaxillary | | 1 | 1 | 1 | 3 |
| Supraclavicular | | 1 | 2 | 2 | 5 |
| Axillary | | 1 | 2 | | 3 |
| Generalized | | | 1 | | 1 |
| Undetermined | | 1 | | | 1 |

This distribution, though the numbers are small, is in accordance with the observation of Grey Turner (11) that tuberculosis of the upper deep cervical lymph nodes, infected presumably by the nasopharyngeal route, is not commonly associated with pulmonary involvement, whereas tuberculosis of axillary or supraclavicular nodes is usually associated with and often preceded by intrathoracic tuberculosis.

Nine of the patients were white and 8 were colored, a distribution approximately equal to that of all patients attending the Institute, which during the years under consideration was in the proportion of five white to four colored patients. Ten were male and 7 female.

The age distribution was as follows:

| | AGE IN YEARS | | | | | | TOTAL |
|---|---|---|---|---|---|---|---|
| | 1–4 | 5–9 | 10–14 | 15–19 | 20–24 | 25 and over | |
| Number of cases | 1 | 2 | 1 | 8 | 1 | 4 | 17 |

It will be noted that the peak of incidence occurred during the period of adolescence, which is considerably later than that usually reported in the United States (8) and found by the writer in England, where in a series of 324 cases the peak of incidence occurred at the age of nine years; but the numbers here are small and the degree of selectivity of the material makes it unsafe to draw any general conclusions.

## COMPARISON WITH OLD RECORDS

In order to determine whether any change had taken place in the incidence of lymph node tuberculosis among patients of the Henry Phipps Institute during the past thirty years, the records were studied of 1,000 patients who attended there successively during the year 1907. Neither tuberculin testing nor roentgenological examination was employed at this time, diagnosis being based on physical examination. About half the patients diagnosed as having pulmonary tuberculosis were found to have tubercle bacilli in their sputum. The figures are as follows:

| | CERVICAL LYMPH NODE TUBERCULOSIS | | | | TOTAL |
|---|---|---|---|---|---|
| | Obsolete | | Active | Negative | |
| | With scars | Without scars | | | |
| Pulmonary tuberculosis | 3 | 3 | 10 | 824 | 840 |
| Abdominal tuberculosis | | | 1 | | 1 |
| No tuberculosis | | | 1 | 124 | 125 |
| Diagnosis not completed | | | | 34 | 34 |
| Total | 6 | | 12 | 982 | 1,000 |

Active tuberculous lymphadenitis was found in 10 out of 840 patients with pulmonary tuberculosis (which in view of the diagnostic methods

available may be regarded as chiefly "moderately advanced" or "far advanced"), that is, 1.2 per cent. The incidence of active tuberculous lymphadenitis in patients of the 1933–1937 series with moderately or far advanced pulmonary tuberculosis was 6 out of 680, that is, 0.89 per cent. The difference is not significant.

Of the 840 patients with pulmonary tuberculosis 6 showed evidence of previous tuberculous lymphadenitis (0.71 per cent). This figure is actually less than that found in the years 1933–1937 (1.38 per cent).

There has been a marked change in the type of patients attending the Institute since 1907, notably in the great increase of colored patients, but no marked clinical difference has been observed in this type of disease as it affects either colored or white patients. It may be that the type of lymph node infection has changed, possibly from a bovine to a human aetiology, and that the form now predominating is more commonly followed by the development of pulmonary tuberculosis than that found thirty years ago. In this earlier material, however, slight errors of observation or recording in two or three cases could alter the figures considerably and diagnosis lacked the corroboration of the X-ray. It is probably safe to conclude that during these thirty years the incidence of previous lymph node tuberculosis in cases of pulmonary tuberculosis has at least shown no decrease, if it has not actually increased.

## SUMMARY AND CONCLUSIONS

1. A series of 5,000 successive patients attending a tuberculosis dispensary during the years 1933–1937 was studied to determine the incidence of tuberculosis of peripheral lymph nodes, and was compared with the records of 1,000 successive patients attending the same clinic in the year 1907.

2. The total number of cases of tuberculous cervical lymphadenitis, active and obsolete, was 51, or 1.02 per cent of all patients examined in the 1933–1937 series, and 18, or 1.80 per cent, in the 1907 series.

3. In the 1933–1937 series, active tuberculosis of the cervical lymph nodes was found in 17 cases, or 0.34 per cent of the patients examined; 4 of these were cases of recrudescent older lesions. The peak of incidence occurred in the 15 to 19 year age-groups. The disease was equally distributed and followed a similar clinical course in white and colored patients. Associated intrathoracic tuberculosis was found in cases of tuberculosis of the supraclavicular and of the axillary groups of lymph nodes, but not in cases where the upper deep cervical lymph nodes alone

were involved. This supports the belief that the former cases were infected by a primarily pulmonary route and the latter by a primarily nasopharyngeal route.

4. Enlargement of cervical lymph nodes, clinically not tuberculous or malignant, was noted in 494 out of 2,746 patients in whom routine roentgenography showed no intrathoracic tuberculosis, and occurred in an approximately equal proportion of tuberculin-positive and tuberculin-negative reactors. There was no evidence of latent or subclinical tuberculosis of cervical lymph nodes in this group.

5. Clinical evidence of obsolete tuberculous cervical lymphadenitis was found in 38 patients in the 1933–1937 series, or 0.76 per cent of all patients examined. This occurred in 1.38 per cent of patients with adult-type pulmonary tuberculosis, more than twice as frequently as in patients in whom roentgenography showed no intrathoracic tuberculosis. This suggests that patients with tuberculous cervical lymphadenitis tend subsequently to develop progressive pulmonary tuberculosis more frequently than patients without tuberculous cervical lymphadenitis.

6. The incidence both of active and obsolete tuberculous cervical lymphadenitis in patients with pulmonary tuberculosis was approximately the same in those attending during 1933–1937 as in those attending in 1907. A lapse of thirty years has apparently not changed the relationship between glandular and pulmonary tuberculosis as manifested in the patients of this clinic.

Acknowledgment is due to Dr. Esmond R. Long, Director of the Henry Phipps Institute, for permission to make this survey and for much helpful advice.

## REFERENCES

(1) Landis, H. R. M.: The disappearance of scrofula, Amer. Rev. Tuberc., 1930, *21*, 195.
(2) Thompson, B. C.: Brit. Med. Jour., 1936, *2*, 584.
(3) Bradbury, F. C. S.: Causal factors in tuberculosis, Natl. Assn. for Prev. Tuberc., London, 1935.
(4) Aronson, J. D.: Personal communication.
(5) Harrington, F. E., Myers, J. A., and Levine, N. M.: Significance of the tuberculin test, Jour. Amer. Med. Assn., 1937, *108*, 1311.
(6) Diagnostic Standards, Natl. Tuberc. Assn., New York, 1935, p. 26.
(7) Long, E. R., Seibert, F. B., and Aronson, J. D.: Tubercle, 1935, *16*, 304.
(8) Miller, R. D.: Tuberculosis of the lymphatic system, New York, 1935.
(9) Marfan, A.: Arch. gén. de méd., 1886, *17*, 423.
(10) Fishberg, M.: Pulmonary tuberculosis, Philadelphia, Pa., 1932, *2*, 31.
(11) Turner, G. G.: Newcastle Med. Jour., 1931, *11*, 145.

# BILATERAL PHRENIC-NERVE INTERRUPTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

ROBERT V. COHEN AND GEORGE WILLAUER

The value of interruption of the phrenic nerve in the treatment of pulmonary tuberculosis is at present a debatable point. There are phthisiologists and thoracic surgeons who believe it a procedure of great importance and who advise widespread use of temporary or permanent paralysis (14, 15, 16). There are other workers who consider the operation a waste of valuable time, productive of little, if any, good and capable of considerable harm (5). The great majority is somewhere between the two camps.

In reviewing the records of over 250 patients at the Eagleville Sanatorium in whom phrenic-nerve interruption was performed by one of us (G. W.) we found eleven cases of bilateral operation, attempted or successful. This constitutes a larger group than has been reported in the literature and for this reason the cases have been subjected to critical analysis.

Bilateral phrenic-nerve interruption is not unknown. Several writers have described it—some as a successful procedure, others as something to be avoided on theoretical or practical grounds. Alexander (1) mentions several cases in which the operation was performed to relieve persistent singultus or to permit artificial respiration in cases of diaphragmatic tetanus.[3] One rather startlingly successful case of Brunner's is quoted in which a left thoracoplasty had to be followed by bilateral novocaine injection of the phrenic nerves because of intractable singultus. Later Alexander (14) mentioned three of his own cases of bilateral crushing operation in which the second crushing was not performed until motion had returned to the diaphragm on the previously operated side. At this time he wrote that he had never employed simultaneous bilateral

[1] From the Eagleville Sanatorium, Eagleville, Pennsylvania.

[2] Presented in part at a meeting of the Laennec Society of Philadelphia, March, 1937.

[3] Since this paper was written an excellent analysis of the question of bilateral operation has appeared in the following: JOHN ALEXANDER, *The Collapse Therapy of Pulmonary Tuberculosis*, Charles C. Thomas, Springfield, Illinois, 1937, pp. 152–154.

temporary interruption for pulmonary tuberculosis and was strongly opposed to bilateral permanent paralysis. Joannides and Schlack (10) have suggested the use of bilateral phrenic interruption and pneumoperitoneum for cases in which bilateral artificial pneumothorax is indicated but impossible. Thus far they have published no results.

O'Brien (15), one of the enthusiasts for phrenic-nerve surgery, mentions bilateral operation and sets up criteria for the type of case that may respond best to this treatment. Schwatt (17) in 1933 collected the available cases from the foreign literature and added one of his own. Duryea (8) contributed one case in which the operation was successfully performed immediately postpartum. This he believed counteracted the deleterious effect of sudden descent of the diaphragm after delivery. Potter, Berry and Bortone (16) report one case of right phrenicotomy followed by left phrenicectomy.

At least five cases of postencephalitic tic of the diaphragm have been treated by bilateral phrenic-nerve surgery (7, 9, 18, 20, 21). In several cases temporary operations were performed which later, after symptoms recurred, had to be made permanent. None of the postencephalitic cases reported suffered any unusual dyspnoea, but it must be remembered that they started with healthy lungs and had no atrophy of the accessory muscles of respiration such as often accompanies chronic pulmonary tuberculosis.

## TECHNIQUE

The only variation from the usual technique is that after exposure of the nerve on the side of the second operation we inject a very small amount of novocaine (0.5 per cent) and observe the patient for at least twenty minutes before crushing the nerve. In two cases there was sufficient dyspnoea to warrant discontinuing further attempts at diaphragmatic paralysis. Neither patient suffered any lasting ill effects. It is interesting to note that in one case the hemidiaphragm was paralyzed for only six hours while the other, with approximately the same amount of surgical handling and novocaine, remained paralyzed for over six weeks.

## SELECTION OF CASES

No information of value was obtained from preoperative and postoperative studies of vital capacity. This measurement is often greatly reduced in patients with only moderately extensive pulmonary tubercu-

losis and may be greater after a successful surgical procedure than it was before. This was true of one man in the present series whose dyspnoea decreased and vital capacity increased following a left phrenic crushing six months after a right phrenic evulsion. One of the disadvantages of any form of phrenic-nerve interruption is the inability to forecast the rise of the diaphragm or, in temporary operations, the duration of paralysis. For this reason we relied more upon dyspnoea as a criterion than change in vital capacity measurements or estimation by roentgenological studies of the volume of nonfunctioning lung tissue. For the same reason we consider the preliminary injection of the nerve with novocaine a very important "test operation."

We do not intend to discuss here the indications and contraindications for phrenic-nerve surgery. Suffice it to say that we considered the indications fulfilled at the time of the first operation. In some cases phrenic interruption was the procedure of choice, in others an operation of necessity, artificial pneumothorax having failed or been found impossible.

In selecting the second operation, artificial pneumothorax was almost always the procedure of choice but, because of reëxpansion or lack of free pleural space, was ineffective. Bed-rest was of course used in all cases. Thoracoplasty was contraindicated in every case by the character, extent and distribution of the disease. The decision to operate was made only after conference of the medical, surgical and roentgenological staff.

## DURATION OF PARALYSIS

The present series is too small to allow drawing any conclusions as to the duration of paralysis of the hemidiaphragm after crushing the phrenic nerve. In the eight cases which lived until after motion of the diaphragm was resumed the average paralysis was 8.5 months with extremes of three and thirteen months.

In one case motion returned to the homolateral leaf of the diaphragm sixteen months after the evulsion of 12 cm. of nerve. This has been noted before (4) but it is not a frequent occurrence.

At the time of the second operation the contralateral hemidiaphragm was still paralyzed in ten of the eleven cases. At the time of discharge six patients had unilateral paralysis of the diaphragm and one had no paralysis.

## RESULTS

The results are summarized in table 1.

In cases 1 and 2, both having had phrenic evulsion on the right side, left phrenic crushing was attempted thirteen and thirty-five months after the first operation. In both cases the preliminary injection of the nerve with novocaine caused enough dyspnoea to preclude further paralysis. In one case the diaphragm resumed motion in six hours in the other it took six weeks. Both patients are still living and showed no permanent good or ill effects after the second attempted operation.

In two far advanced cases (cases 3 and 4) the second operation was done solely for palliative reasons. One was a right phrenic crushing ten months after a left phrenic evulsion, the other a left crushing thirteen months after a right evulsion. In both cases artificial pneumothorax was impossible, dyspnoea severe, haemoptyses profuse and cough was almost incessant. In case 4 there was marked retraction of the mediastinum to the left. In each case the symptoms, especially cough, were noticeably relieved but the disease continued its natural course and the patients died one and two months after the second operation.

In cases 5 and 6 the second operation was performed because of late spread of the disease twenty-eight and forty months after a right phrenic evulsion. Artificial pneumothorax had been found impossible in both these patients. There was no dyspnoea or discomfort following complete paralysis of the diaphragm which lasted three and thirteen months. In neither case was the course of the disease affected. One patient died seventeen months after the second operation. The other is at home doing light housework. She still has positive sputum but no other symptoms.

One patient (case 7) had a left phrenic crushing five months after a right evulsion. There was marked clinical improvement during the next nine months during which both leaves of the diaphragm were paralyzed. When the left hemidiaphragm resumed motion the tuberculous processes in the left lung became active again. We hesitated to perform a permanent operation because of the paralysis and high position of the right dome of the diaphragm. However, sixteen months after the right evulsion (12 cm. of nerve evulsed, no accessories seen) the right dome resumed motion. A left phrenic evulsion was performed, followed by marked clinical improvement and disappearance of cavities. The patient went home against advice and married. Nineteen months

TABLE 1

| CASE | FIRST OPERATION | DURATION OF PARALYSIS | INTERVAL BETWEEN OPERATIONS | SECOND OPERATION | DURATION OF PARALYSIS | RESULT |
|---|---|---|---|---|---|---|
| 1. T. W. | Right evulsion | Permanent | 13 months | Left crushing unsuccessful | 6 weeks | No effect. Discharged |
| 2. N. B. | Right evulsion | Permanent | 35 months | Left crushing unsuccessful | 6 hours | No effect. Discharged |
| 3. A. V. | Left evulsion | Permanent | 10 months | Right crushing | | Palliated. Died in two months |
| 4. R. B. | Right evulsion | Permanent | 13 months | Left crushing | | Palliated. Died in one month |
| 5. S. G. | Right evulsion | Permanent | 28 months | Left crushing | 13 months | No effect. Died in seventeen months |
| 6. M. M. | Right evulsion | Permanent | 40 months | Left crushing | 3 months | No effect. Discharged. General condition excellent. Sputum positive |
| 7. E. L. | Right evulsion | 16 months | 5 months | Left crushing | 9 months | Improved. Discharged |
| | | | 11 months after left crushing | Left evulsion | Permanent | Original cavities closed. New one developed later. General condition good. Sputum positive |
| 8. J. A. | Right evulsion | Permanent | 23 months | Left crushing | 9 months | Died four months after left evulsion |
| | | | 10 months after left crushing | Left evulsion | | |
| 9. M. T. | Left crushing | 13 months | 12 months | Right evulsion | Permanent | Improved. General condition excellent. Sputum positive |
| 10. S. B. | Right evulsion | Permanent | 6 months | Left crushing | 9 months | Improved. Discharged. General condition good. Sputum positive |
| 11. D. L. | Right crushing | 4 months | 5 months | Left crushing | 7 months | Improved. Discharged. Both domes moving. Sputum negative for over two years |

later a new cavernous process developed in the left lower lobe. The old lesions remained inactive and were invisible on X-ray films. The man is still at home and has no symptoms except the expectoration of a small amount of positive sputum. The right lung is inactive, all cavities invisible, the diaphragm moving freely. The left lung has a fresh active lower lobe cavity. Further surgery is indicated in this case and will be done if the patient can be persuaded to return to the Sanatorium.

The remaining four cases (three good results and one death) are quite interesting and deserve to be reported in some detail.

*Case 8:* J. A., male, white, 22 years old, was admitted to the Eagleville Sanatorium in January, 1933 with pulmonary tuberculosis of five years' duration, four of which had been spent in other sanatoria. Artificial pneumothorax had been attempted unsuccessfully on the right side in an effort to control frequent profuse haemoptyses. On admission the patient was not toxic and had few symptoms. There was a large cavity in the right upper lobe and some fibroproliferative tuberculosis in the left upper lobe (figure 1a). Sputum was positive.

Shortly after admission the patient had a severe haemoptysis. Artificial pneumothorax was attempted on the right side but could not be induced. On March 6, 1933 a right phrenic evulsion was performed. There was marked improvement during the next seventeen months. Sputum, though scanty, remained positive. In August, 1934 the patient had almost daily haemoptyses of 100 cc. or more. There were clinical signs of activity in the left upper lobe. X-ray films were suggestive but not absolutely certain of recent cavity formation in the same region (figure 1b). Left artificial pneumothorax was attempted twice. On each occasion there was a free pleural space and small amounts of gas were injected without difficulty. However, each time the patient showed alarming cyanosis and dyspnoea and the gas had to be aspirated. Careful fluoroscopic examination showed that on neither occasion was there a complete (traumatic) pneumothorax. Haemoptyses continued. On February 13, 1935 a left phrenic crushing was performed. There was little rise of the diaphragm but the left leaf remained paralyzed for nine months. During these months there was no haemoptysis and the sputum remained consistently negative (figure 1c). The patient was not dyspnoeic and appeared to be on the road to complete recovery.

In November, 1935 the left dome of the diaphragm resumed motion and the sputum was again positive (figure 1d). Accordingly, in December, 1935 the left phrenic nerve was evulsed. There was little change in the level of the left hemidiaphragm. Shortly after this operation the old cavity in the right upper lobe was again visible on X-ray films. The patient became progressively

more dyspnoeic and cyanotic. There was clinical evidence of right ventricular failure. This is also noticeable by comparing figures 1d and 1e which show an increase in the size of the right heart shadow shortly after the left phrenic evulsion.

The patient went down-hill rapidly. Haemoptysis was frequent and profuse. Posthaemorrhagic bronchopneumonia developed and the patient died as a result of this and cardiac failure on April 26, 1936, four months after the last phrenic operation.

Autopsy revealed a 2 cm. cavity in the right upper lobe, no active foci in the left lung, bilateral lower lobe posthaemorrhagic bronchopneumonia. There was hypertrophy and dilatation of the heart, especially of the right ventricle and pulmonary conus. The pericardium, myocardium and valves were normal. The diaphragm appeared atrophied grossly, but microscopically showed only a mild degeneration of the muscle fibres. There was no evidence of hernia or eventration.

*Case 9:* M. T., white, male, 21 years old, was admitted to the Eagleville Sanatorium on June 6, 1932 with advanced cavernous tuberculosis, cavity in the right upper lobe measuring 6 cm. in diameter. The disease was of two years' duration. Artificial pneumothorax was instituted on the right side shortly after admission. The cavity decreased in size but did not disappear. In August, 1933 a small cavity appeared in the apex of the left lower lobe. Shortly after this the patient left the institution and married. The artificial pneumothorax was continued, but by December, 1934 the cavity in the left lower lobe was 4 cm. in diameter and the patient sought readmission (figure 2a).

---

FIG. 1a. Case 8. J. A. January 20, 1933. Condition on admission: tuberculosis of five years' duration; frequent haemoptyses; positive sputum; large cavity in right upper lobe; fibroproliferative tuberculosis, left upper lobe.

FIG. 1b. Case 8. J. A. October 11, 1934. Nineteen months after right phrenic evulsion. There was marked improvement for seventeen months; for the past two months patient had frequent haemoptyses. Right upper lobe quiet, cavity seems to be disappearing. Clinical signs of activity in left upper lobe. X-ray suggestion of fresh active lesion in left upper lobe. Sputum positive.

FIG. 1c. Case 8. J. A. March 9, 1935. Three weeks after left phrenic crushing. Both leaves of diaphragm elevated and fixed. Patient not dyspnoeic. No cavities visible on either side. Sputum consistently negative during the nine months of complete diaphragmatic paralysis.

FIG. 1d. Case 8. J. A. November 7, 1935. Left dome of diaphragm has resumed motion. Sputum again highly positive.

FIG. 1e. Case 8. J. A. January 3, 1936. Sixteen days after left phrenic evulsion. The old cavity in the right upper lobe is again visible. Note the enlargement of the cardiac silhouette (right ventricle and pulmonary conus) as compared with fig. 1d. Patient died of right ventricular failure and posthaemorrhagic bronchopneumonia three and one-half months after this film was taken.

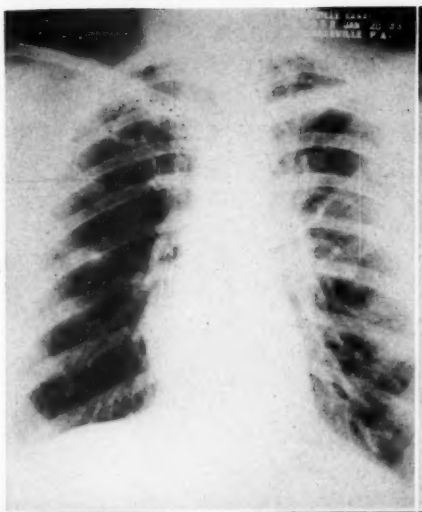


FIG. 1a

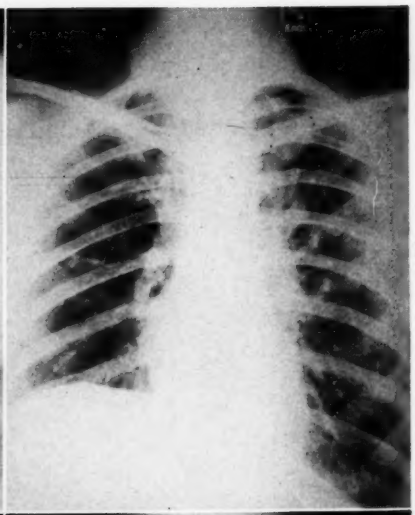


FIG. 1b

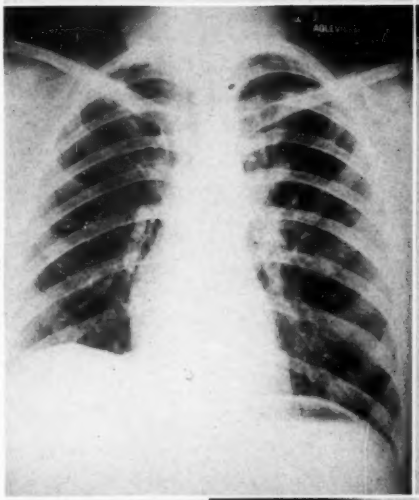


FIG. 1c

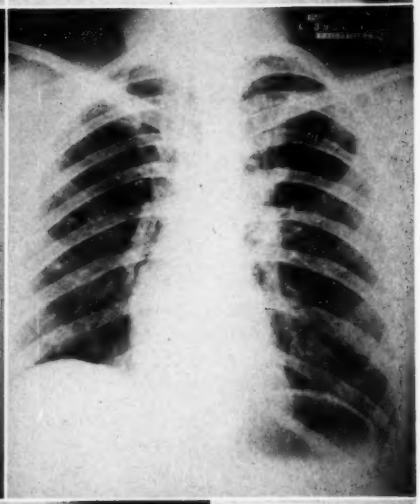


FIG. 1d

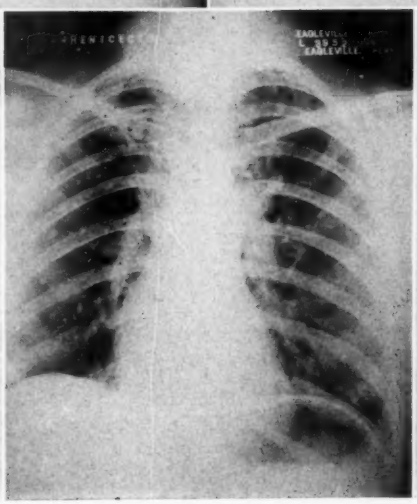


FIG. 1e

FIG. 2a

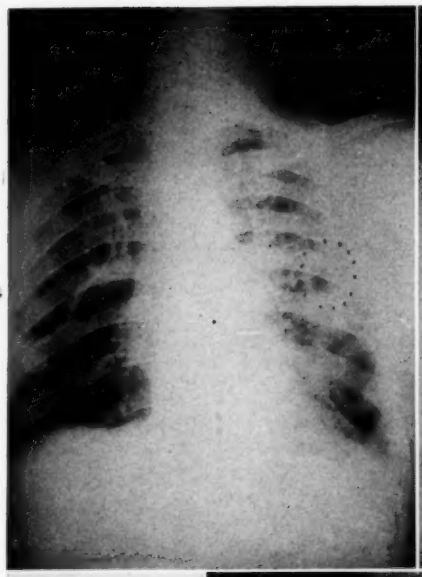


FIG. 2b

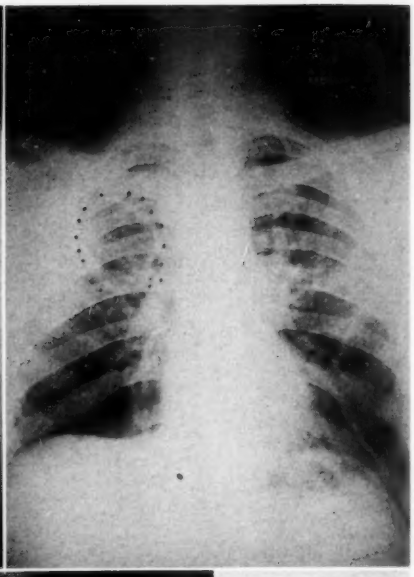


FIG. 2c

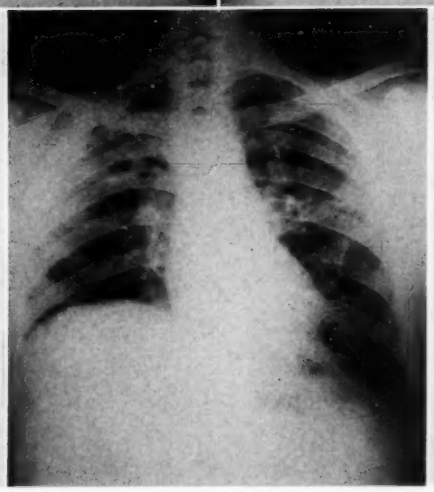


FIG. 2a. Case 9. M. T. December 18, 1934. Pulmonary tuberculosis of four and one-half years' duration. Right artificial pneumothorax for over two years. Large fresh excavation at apex of left lower lobe. Sputum positive.

FIG. 2b. Case 9. M. T. January 16, 1936. One year after left phrenic crushing. The cavity on that side has disappeared. During the past five months the right artificial pneumothorax slowly obliterated and the original large cavity reappeared. Sputum positive.

FIG. 2c. Case 9. M. T. June 17, 1937. Eighteen months after right phrenic evulsion. No cavities visible in either lung. General condition excellent. Sputum positive only by concentration methods.

A left phrenic crushing was performed on January 19, 1935. There was no rise in the hemidiaphragm, but it was paralyzed for thirteen months. The cavity diminished in size.

In August, 1935 the right artificial pneumothorax slowly obliterated and the original large cavity reappeared (figure 2b). The patient was readmitted to the Sanatorium and a right phrenic evulsion was performed on January 31, 1936. There was slow but steady improvement in both lungs after the second operation. At present the patient is nontoxic, overweight, suffers no dyspnoea. Both lungs are greatly improved. He expectorates a small amount of sputum which is usually positive (figure 2c).

*Case 10:* S. B., white, male, 28 years old, was admitted to the Eagleville Sanatorium on April 6, 1934 with pulmonary tuberculosis of three and one-half years' duration. There was advanced, diffuse, fibroproliferative, cavernous tuberculosis of both upper lobes, more active on the right side (figure 3a). The pleura was so thick that artificial pneumothorax was not attempted. After seven months of bed-rest, during which time there was some improvement a right phrenic evulsion was performed on November 14, 1934.

In February, 1935 there was a spread to the left lower lobe with a rather severe pleurisy (figure 3b). A left phrenic crushing was performed on May 1, 1935. The left dome was elevated 3 cm. at first (figure 3c) and came down slowly until motion returned in February, 1936, nine months after operation. Except for the immediate postoperative period there was less dyspnoea after the second operation than before it. Sputum was negative during most of the nine months of bilateral paralysis, but became positive again shortly after motion of the left hemidiaphragm was resumed.

The patient was discharged in October, 1936 and is still at home. His last film shows more fibrosis than ever in both upper lobes (figure 3d). Sputum is still positive.

*Case 11:* D. L., white, female, 20 years old, was admitted to the Eagleville Sanatorium on August 14, 1933 with pulmonary tuberculosis of fourteen months' duration. The patient was quite toxic, febrile, 26 pounds underweight, and sputum was profuse and highly positive. There was clinical and X-ray evidence of bilateral, advanced, cavernous tuberculosis (figure 4a).

For the first fourteen months she was kept at absolute rest. There was some improvement in both lungs. This was more marked on the left side where a transient bronchopneumonic spread with pleural effusion had occurred.

By November, 1934 the patient was overweight, much less toxic, but her sputum was still profuse and positive (figure 4b). It was decided that a right temporary phrenic interruption might speed resolution and recovery in that lung. This was performed on November 11, 1934. The right hemidiaphragm

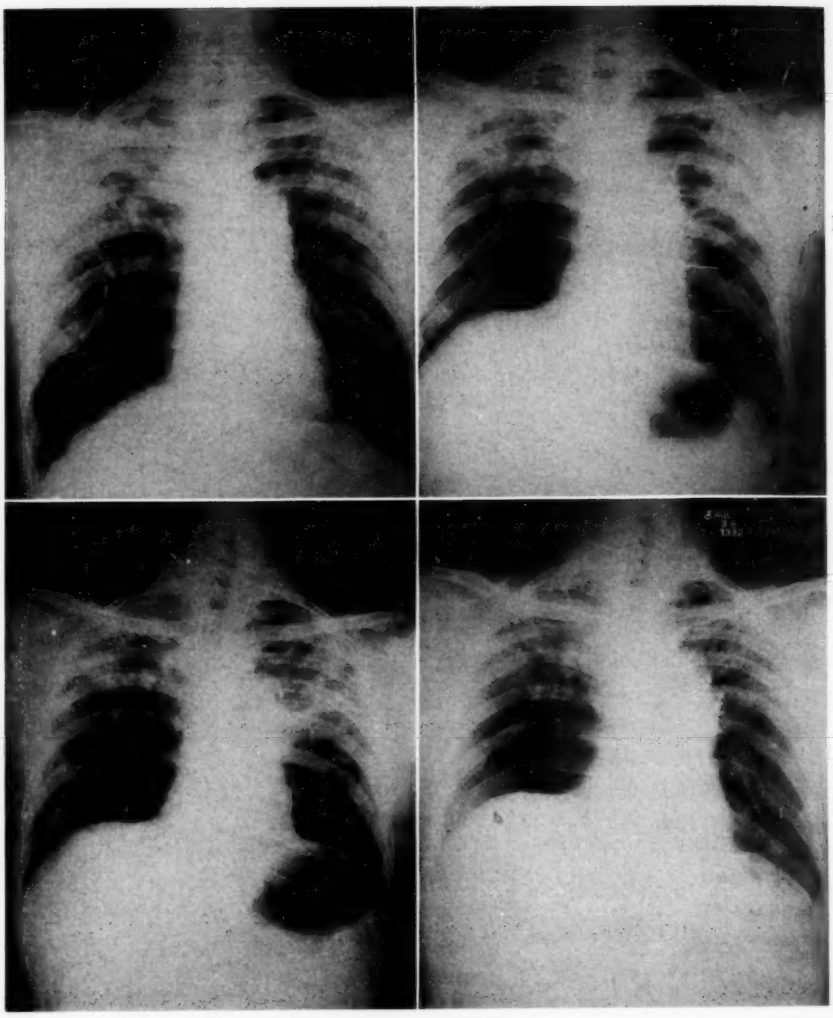


FIG. 3a

FIG. 3b

FIG. 3c

FIG. 3d

FIG. 3a. Case 10. S. B. November 13, 1934. Pulmonary tuberculosis for four years. Advanced, diffuse, fibroproliferative, cavernous tuberculosis of both upper lobes. Very thick pleura. Emphysema of lower lobes. Little improvement on bed-rest. Sputum positive.

FIG. 3b. Case 10. S. B. March 14, 1935. Four months after right phrenic evulsion. Right upper lobe processes are more fibrotic. There has been a spread on the left side. Sputum positive.

FIG. 3c. Case 10. S. B. May 9, 1935. Eight days after left phrenic crushing. Both halves of diaphragm elevated and paralyzed. Patient up and around without unusual dyspnoea. The sputum was negative during most of the nine months of complete paralysis of the diaphragm.

FIG. 3d. Case 10. S. B. April 7, 1937. Patient at home. Sputum positive. No other symptoms. The left hemidiaphragm has been moving for fourteen months. The tuberculous processes in both upper lobes appear more fibrous than at any time in the past.

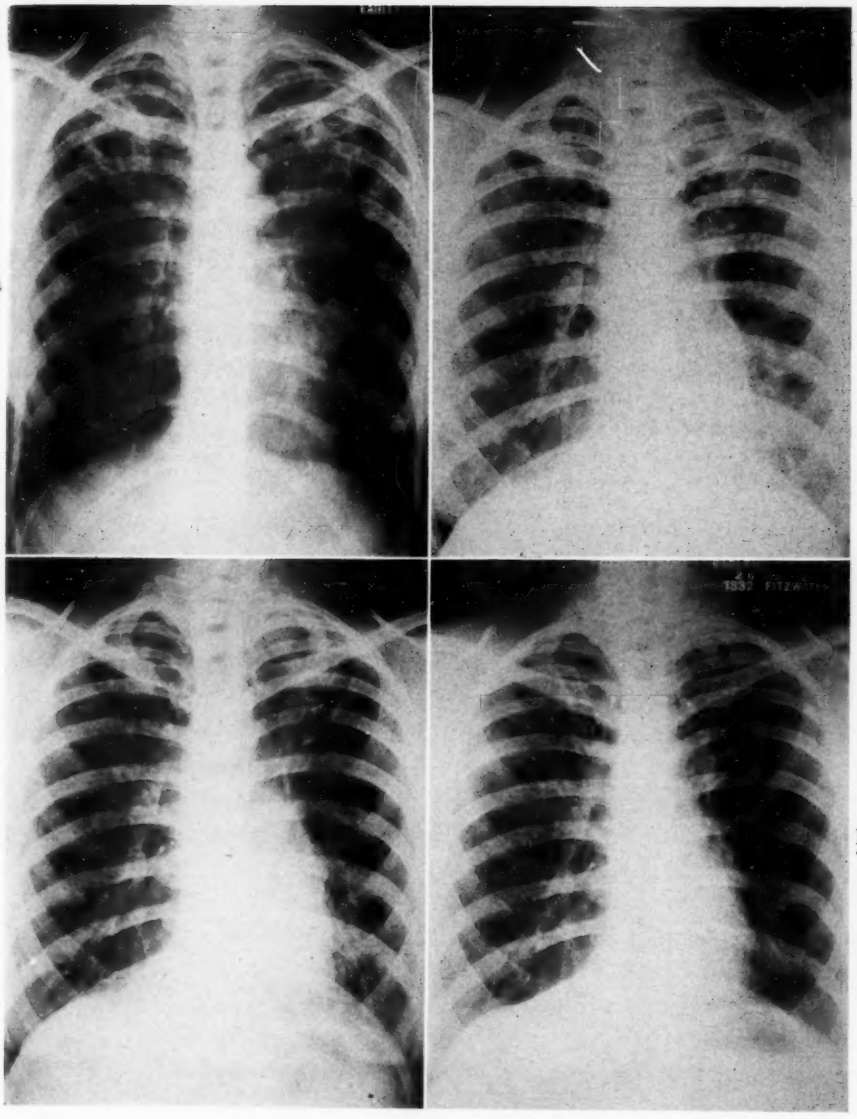


FIG. 4a

FIG. 4b

FIG. 4c

FIG. 4d

FIG. 4a. Case 11. D. L. August 15, 1933. Condition on admission: bilateral, advanced, cavernous tuberculosis; disease of fourteen months' duration; sputum highly positive.

FIG. 4b. Case 11. D. L. November 1, 1934. Improvement on both sides after fourteen months' bed-rest. Some cavities remain in both upper lobes. Sputum positive.

FIG. 4c. Case 11. D. L. March 5, 1935. Four months after right phrenic crushing. The right hemidiaphragm was never elevated but was fixed for four months. Marked improvement on right side. Open cavities still visible in left upper lobe.

FIG. 4d. Case 11. D. L. May 5, 1937. Within five weeks of film shown in fig. 4c a left phrenic crushing was performed. The left hemidiaphragm was slightly elevated and paralyzed for seven months. Within one month of the second operation the sputum turned negative and has remained negative for over two years. Latest follow-up film shows a little fibrosis in both upper lobes. No evidence of cavitation or active disease.

was never appreciably elevated but remained fixed and showed paradoxical movement for four months. There was noticeable clinical improvement and X-ray evidence of clearing in the right upper lobe. The left upper lobe was still active (figure 4c).

On April 10, 1935 a left phrenic crushing was performed. Within one month after operation the sputum turned negative. All cavities completely disappeared within seven months. The left hemidiaphragm was slightly elevated and paralyzed for seven months. The patient was discharged in November, 1935 in excellent condition. Both leaves of the diaphragm were moving freely and no active processes could be demonstrated in either lung. She has been seen regularly since discharge, is symptom-free and has consistently negative sputum (figure 4d).

## COMMENT

In all, the operation was attempted eleven times. It could not be completed twice because of dyspnoea when the second nerve was injected with novocaine. Neither case suffered any permanent ill effects. In two hopelessly advanced cases the operation was done for palliative reasons. There was symptomatic relief but no arrest or retardation of the disease process. In two cases there was no discernible effect on the course of the disease nor any dyspnoea or other untoward symptoms.

Of the remaining five, three were helped considerably by the operation and are at present at home either stationary or making slow progress toward recovery. Another was helped by a temporary operation but died after the paralysis was made permanent. There is without doubt a cardiac factor in this case as roentgen films, as well as clinical and postmortem evidence, point to progressive failure of the right side of the heart following the second permanent operation.

The last patient, who seemed almost hopeless on admission and for many months afterward, is now at home symptom-free with a negative sputum and a very innocent looking X-ray.

It is understood that bilateral phrenic paralysis especially if permanent is not without risk (2, 3). Atrophy of the diaphragm is to be expected (22) although Meade (12) has shown experimentally that tensile strength is not necessarily impaired. Acute dilatation of the stomach (23), interposition of the colon (19) and other serious aftereffects (6) have been reported following unilateral operations. Fortunately we did not experience any of these in our series of cases. We had one case of severe right heart dilatation and believe this must be added to the list of potential complications (13).

There is no question in our minds that bilateral interruption of the phrenic nerve is far from an ideal procedure. Undoubtedly in each of the eleven cases cited, if the patients had been seen at an earlier date or had consented to operation when first proposed, some more effective procedure might have succeeded. However, when seen none were candidates for thoracoplasty. Artificial pneumothorax had been found impossible in some and had reëxpanded in others. Bed-rest was tried in all. It was only when all ordinary measures had failed or been found inapplicable that bilateral phrenic interruption was done. Considering the very poor prognosis of these cases if untreated, we believe the results are far from discouraging.

## CONCLUSIONS

1. Bilateral phrenic-nerve interruption was attempted in eleven cases of pulmonary tuberculosis.

2. Injection of the second nerve with novocaine preliminary to crushing provoked sufficient dyspnoea in two cases to preclude further paralysis.

3. Two hopeless cases were palliated, two others were improved, four were definitely improved, one improved temporarily and later died of tuberculosis and right ventricular failure.

4. The operation should be considered in carefully selected cases unsuitable for artificial pneumothorax or thoracoplasty and not improving on bed-rest.

## REFERENCES

(1) Alexander, J.: The surgery of pulmonary tuberculosis, Lea & Febiger, 1925, p. 185.
(2) Ballon, H. C., Wilson, H. M., Singer, J. J., and Graham, E. A.: Esophagus, stomach and heart following unilateral phrenicectomy, Arch. Surg., 1930, *21*, 1291.
(3) Berry, F. B.: The unfavorable results of phrenicectomy, Ibid., 1930, *21*, 1125.
(4) Boza, M. R. M.: Does function of the diaphragm return in phrenicectomized patients? Rev. Med. Habana, 1936, *47*, 1103. (Abstract Jour. Amer. Med. Assn., 1937, *108*, 80.)
(5) Coryllos, P. N., and Ornstein, G. G.: The management of bilateral cavernous pulmonary tuberculosis, Jour. Thor. Surg., 1936, *5*, 337.
(6) Davies, H. M.: General principles of the surgical treatment of pulmonary tuberculosis, Ibid., 1935, *5*, 113.
(7) Dowman, C. E.: Relief of diaphragmatic tic following encephalitis by section of the phrenic nerves, Jour. Amer. Med. Assn., 1927, *88*, 95.
(8) Duryea, A. W.: Pregnancy and bilateral phrenic exairesis postpartum, Amer. Rev. Tuberc., 1931, *24*, 256.
(9) Gamble, C. J., Pepper, O. H. P., and Mueller, G. P.: Postencephalitic tic of the diaphragm, pulmonary overventilation and relief by blockade of the phrenic nerves, Jour. Amer. Med. Assn., 1925, *85*, 1485.

(10) JOANNIDES, M., AND SCHLACK, O. C.: Phrenic neurectomy and artificial pneumoperitoneum, Jour. Thor. Surg., 1936, *6*, 218.
(11) LAMBERT, A. V. S.: Results of phrenic operations, Ibid., 1934, *4*, 49.
(12) MEADE, R. H., JR.: The tensile strength of the paralyzed diaphragm, Ibid., 1933, *2*, 503.
(13) MOSCHCOWITZ, E.: Hypertension in the pulmonary circulation, Amer. J. Med. Sc., 1927, *174*, 388.
(14) NEHIL, L. W., AND ALEXANDER, J.: An estimate of the value of phrenic nerve interruption for phthisis based on 654 cases, Jour. Thor. Surg., 1933, *2*, 549.
(15) O'BRIEN, E. J.: The choice of procedure in collapse therapy, Ibid., 1935, *5*, 123.
(16) POTTER, B. P., BERRY, F. B., AND BORTONE, F.: Phrenic interruption in the treatment of pulmonary tuberculosis. A five year study and follow-up, Ibid., 1937, *6*, 424.
(17) SCHWATT, H.: Bilateral phrenic exairesis, Amer. Rev. Tuberc., 1933, *28*, 165.
(18) SKILLERN, P. G.: Tic of the diaphragm (postencephalitic) relieved by resection of the phrenic nerves, Jour. Amer. Med. Assn., 1931, *96*, 2098.
(19) SLAVIN, P.: Interposition of the colon following induced phrenic paralysis, Amer. J. Roent., 1935, *33*, 480.
(20) SMITH, H.: Diaphragmatic tic relieved by section of the phrenic nerves, Amer. J. Med. Sc., 1932, *183*, 857.
(21) SPIERS, G. O.: Encephalitic diaphragmatic spasm treated by phrenicectomy, Jour. Nerv. & Ment. Dis., 1929, *69*, 407.
(22) STANBURY, W. S.: Anatomical changes in the diaphragm following phrenicectomy, Amer. Rev. Tuberc., 1934, *29*, 528.
(23) THOMAS, C. A., AND HARPER, F. R.: Acute dilatation of the stomach following left-sided phrenic paralysis and thoracoplasty, Jour. Thor. Surg., 1936, *5*, 507.

# SEX DIFFERENCES IN TUBERCULOSIS MORTALITY IN THE UNITED STATES[1]

C. C. DAUER[2]

Sex differences in mortality from tuberculosis have for many years been the subject of much discussion and study but the explanation for these differences has not been agreed upon. Most studies have been limited to certain sections of the United States, particularly the Registration Area of 1900, 1910 or 1920. Putnam (1) in 1927 reported an extensive study of sex differences in mortality for the Registration Area of 1900 from 1870 to 1920 in which environmental and biological factors were discussed in relation to their possible influence on mortality and a review of the important literature up to that time was made. It is the purpose of this paper to point out certain variations in tuberculosis mortality among males and females which now exist in different sections of the entire country.

In some sections of the United States there has been a gradual change in the sex ratio of tuberculosis mortality since the middle of the nineteenth century. In Massachusetts and Rhode Island where data on deaths by sex are available since about 1850 and 1860 respectively, female death rates were in excess of males previous to 1890, but at the present time conditions are reversed. The same change has taken place in New York City since the Civil War and in the white population of Baltimore, Maryland, since 1875. However, similar changes have not taken place in all parts of the United States. For instance, in Charleston, South Carolina, the mortality rate for white males has remained higher than for females since 1820. On the other hand, in the State of Indiana female mortality has exceeded that for males since 1890.

## DESCRIPTION OF DATA USED IN THIS REPORT

Mortality data used in this report were taken from unpublished tabulations made in the Division of Vital Statistics, Bureau of the Census,

[1] Presented at a session of the Social Work Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] Department of Preventive Medicine, Graduate School of Medicine and School of Medicine, Tulane University of Louisiana, New Orleans, Louisiana.

Washington, D. C. The author wishes to express his appreciation to the Bureau of the Census for permission to use this material. All information on population, birth rates, occupation, etc., was taken from published reports of the Bureau of the Census.

The data on mortality are for the four-year period from 1931 to 1934 inclusive, for all States except Texas, whose data are for the years 1933 and 1934.

All data for Maryland, District of Columbia, Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Alabama, Mississippi, Arkansas, Louisiana, Oklahoma, Texas and California are for white persons only, whether they refer to mortality rates, ratios, occupation, birth rates or other information. For all other States tabulated data are those for the total population. Consequently, this study is essentially one on sex differences in the white population of the United States.

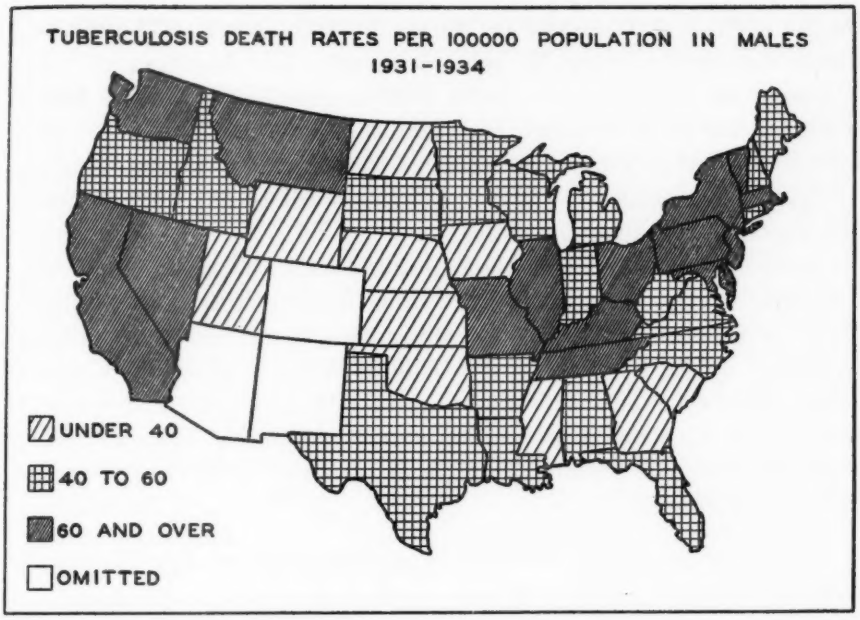
Although rates for Colorado, Arizona and New Mexico are given in table 1, these States have been omitted when making comparisons or calculating coëfficients of correlation because of the large percentage of nonresident tuberculosis deaths occurring in these States.

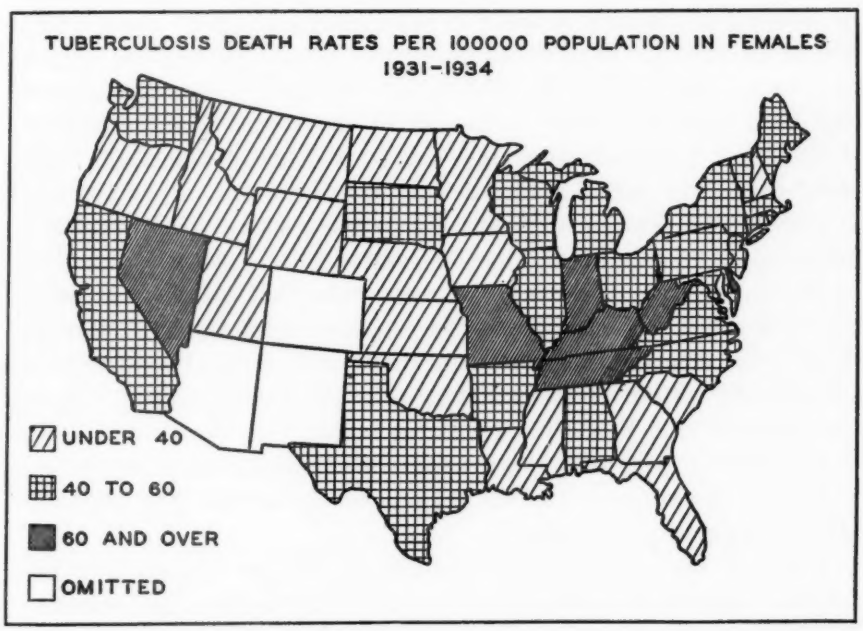
## DIFFERENCES IN MORTALITY FOR ALL AGES

In a recent publication (2) in which the regional distribution of tuberculosis mortality for the white population by counties for the entire country was shown, we pointed out the areas where mortality is comparatively high. A study of mortality by sex for each of the States shows that States with a relatively high mortality for males and females are generally to be found in the regions where tuberculosis death rates by counties are relatively high. However, both male and female rates are not necessarily high in all areas where large groups of counties show a high mortality. For instance, in the northeastern section of the country only the male rates are relatively high.

In regions of low mortality, as shown in our study of mortality by counties, sex differences are equally apparent. In some of these areas, although male and female rates are much below the average, the excess of male over female mortality is marked while in other regions of low mortality the rates for each sex are about equal.

The States which have relatively high tuberculosis mortality rates for males are in two groups, the Northeastern and Western. The northeastern group includes the States from Missouri to Massachusetts


TUBERCULOSIS DEATH RATES PER 100000 POPULATION IN MALES
1931-1934
UNDER 40
40 TO 60
60 AND OVER
OMITTED


TUBERCULOSIS DEATH RATES PER 100000 POPULATION IN FEMALES
1931-1934
UNDER 40
40 TO 60
60 AND OVER
OMITTED

on the north and Tennessee to Maryland on the south. The Western States include California, Nevada, Washington and Montana.

Except for Nevada, the States with a comparatively high female mortality are located in the east central part of the country. They include Kentucky, Tennessee, Indiana, Missouri, West Virginia, Virginia, Maryland and Delaware. Male tuberculosis death rates are also above the average in all of these States.

Another interesting point about mortality for all ages by sex is the difference in ratio of male to female rates in different sections. In general, the ratio of male to female mortality is high (male rates greatly in excess) in the New England, Middle Atlantic, East North Central, Rocky Mountain and Pacific Coast States. In the West North Central, West South Central, East South Central and South Atlantic States, male ratios are comparatively low, that is, female rates about equal to or in excess of males.

## SEX DIFFERENCES IN TUBERCULOSIS MORTALITY BY AGE GROUPS

In discussing variations in mortality by sex and age for individual States, comparisons will be made of broad age groups rather than of five or ten-year age groups in order to save space and time. Four groups will be used: under 10 years, 10 to 30 years, 30 to 55 years, and 55 years and over. The first group presumably includes only deaths due to childhood type of disease. The second covers the period when the disease most frequently appears in adolescents and young adults. The third covers the period of middle life and the fourth of old age. Although this is obviously an arbitrary grouping a study of five or ten-year subgroups shows essentially the same variations.

*Under 10 years:* The mortality rates from 1931 to 1934, inclusive, for each sex varied considerably in different sections of the country. The highest mortality occurred in the Middle Atlantic, East North Central and certain Western States, while the lowest rates occurred in the Southern and West North Central States.

The ratio of male to female mortality was fairly constant in different sections of the country. In the majority of States the male rates were slightly in excess of the female.

*Ten to 30 years:* Tuberculosis mortality in this age was relatively high for both sexes in the northeastern section of the country, and relatively low in the southern section.

The earlier appearance of tuberculosis of the reinfection type in ado-

lescent and young adult females has been emphasized in numerous reports and discussions. The study which we are now reporting indicates that young females experienced a higher rate of mortality in all parts of the country than males of the same age. Even though the rates for males 10 to 30 years of age exceeded that of females in the same broad age group in Idaho, Montana and Utah, this excess was not present in the group from 15 to 25 years of age. In the West North Central, Rocky Mountain and Pacific Coast States mortality rates in young adult females did not exceed those for young adult males by so great a margin as in other sections. This relatively high ratio of male to female rates in these States seems to have been the result of a lower rate of mortality among females rather than relatively higher rates among males in this particular age group.

*Thirty to 55 years:* There was considerable variation in male mortality for this age in the different sections of the country while female rates were much more constant. In the Northeastern States male mortality was higher than in other sections.

The rates for males in this group exceeded those for females in all but a few States. In the West North Central and Southern States the female rates nearly equaled and in a few instances exceeded those of males. However, in the northeastern section and Western States the excess of male over female mortality was about 50 per cent.

*Fifty-five years and over:* In this old age group the male rates were more constant while those for females varied to a considerable degree in different sections. The female rates in Southern States were relatively high in comparison with other sections of the country, and while male mortality was also high in this area it did not exceed that for males in other sections by so great a margin.

In the extreme northeastern section and far Western States the male rates were approximately twice as high as the female, while in the Southern States female mortality was higher in many States than that for males. The characteristic feature about mortality in Southern States for the last decade has been the high rate in old age for both sexes, a fact which has been pointed out in a previous study (3).

## CORRELATION OF ENVIRONMENTAL, SOCIAL AND BIOLOGICAL FACTORS WITH TUBERCULOSIS MORTALITY IN MALES AND FEMALES

We are confronted with numerous complicated and often inconstant factors when trying to give any explanation for sex differences in a given

## TABLE 1

*Tuberculosis mortality rates per 100,000 population by sex and age, and ratio of male to female rates, 1931–1934*

| | ALL AGES | | | UNDER 10 YEARS | | | 10–30 YEARS | | | 30–55 YEARS | | | 55 YEARS AND OVER | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Ratio Male / Female | Male | Female | Ratio Male / Female | Male | Female | Ratio Male / Female | Male | Female | Ratio Male / Female | Male | Female | Ratio Male / Female |
| Registration Area | 56.2 | 45.2 | 1.24 | 10.7 | 9.5 | 1.22 | 28.6 | 41.8 | .69 | 84.8 | 51.5 | 1.64 | 113.0 | 71.9 | 1.57 |
| Maine | 46.6 | 44.2 | 1.05 | 12.7 | 8.9 | 1.43 | 33.2 | 58.5 | .57 | 67.0 | 46.5 | 1.44 | 74.0 | 52.3 | 1.41 |
| New Hampshire | 47.9 | 38.2 | 1.25 | 13.7 | 9.1 | 1.51 | 25.3 | 38.3 | .66 | 67.9 | 45.0 | 1.51 | 90.6 | 53.0 | 1.70 |
| Vermont | 67.3 | 45.6 | 1.47 | 15.1 | 11.2 | 1.35 | 27.0 | 44.1 | .61 | 102.9 | 58.2 | 1.76 | 144.0 | 68.0 | 2.11 |
| Massachusetts | 64.2 | 45.0 | 1.43 | 15.3 | 14.6 | 1.04 | 36.1 | 54.0 | .67 | 98.0 | 50.8 | 1.94 | 111.3 | 45.2 | 2.46 |
| Rhode Island | 63.6 | 43.8 | 1.45 | 21.1 | 17.9 | 1.18 | 32.2 | 49.0 | .66 | 93.1 | 48.5 | 1.92 | 131.1 | 52.6 | 2.48 |
| Connecticut | 54.8 | 42.3 | 1.29 | 15.8 | 10.1 | 1.56 | 35.2 | 50.2 | .70 | 89.5 | 48.5 | 1.85 | 108.1 | 48.0 | 2.25 |
| New York | 78.5 | 49.3 | 1.59 | 19.8 | 15.8 | 1.25 | 44.4 | 56.2 | .79 | 116.9 | 54.7 | 2.14 | 141.5 | 57.8 | 2.45 |
| New Jersey | 69.5 | 50.9 | 1.37 | 14.2 | 13.0 | 1.09 | 41.3 | 59.4 | .71 | 104.4 | 58.1 | 1.80 | 133.0 | 59.2 | 2.24 |
| Pennsylvania | 62.5 | 47.6 | 1.31 | 15.1 | 12.5 | 1.21 | 36.5 | 54.4 | .65 | 98.2 | 54.7 | 1.80 | 119.5 | 65.1 | 1.83 |
| Ohio | 62.3 | 51.9 | 1.20 | 14.6 | 14.0 | 1.04 | 42.2 | 60.3 | .70 | 91.6 | 56.4 | 1.62 | 102.8 | 70.0 | 1.47 |
| Indiana | 58.5 | 60.7 | .97 | 15.2 | 12.5 | 1.21 | 37.3 | 60.0 | .62 | 80.0 | 60.0 | 1.33 | 111.4 | 110.0 | 1.01 |
| Illinois | 66.5 | 48.7 | 1.34 | 14.7 | 13.2 | 1.11 | 42.8 | 55.0 | .78 | 97.9 | 55.3 | 1.77 | 103.7 | 60.0 | 1.73 |
| Michigan | 55.8 | 45.1 | 1.24 | 16.8 | 17.2 | .98 | 38.8 | 57.3 | .68 | 83.7 | 48.2 | 1.73 | 86.8 | 46.6 | 1.86 |
| Wisconsin | 49.0 | 46.3 | 1.06 | 9.7 | 10.7 | .91 | 27.4 | 44.5 | .62 | 76.5 | 47.8 | 1.60 | 85.0 | 53.8 | 1.58 |
| Minnesota | 42.5 | 36.2 | 1.18 | 8.8 | 8.4 | 1.04 | 25.5 | 37.2 | .69 | 65.6 | 42.1 | 1.55 | 73.8 | 50.8 | 1.45 |
| Iowa | 26.7 | 29.2 | .91 | 5.6 | 5.5 | 1.02 | 16.9 | 19.6 | .86 | 37.0 | 36.5 | 1.01 | 52.6 | 51.5 | 1.02 |
| Missouri | 72.7 | 60.4 | 1.20 | 15.9 | 15.8 | 1.01 | 44.0 | 62.9 | .70 | 103.8 | 63.2 | 1.64 | 135.6 | 99.0 | 1.36 |
| North Dakota | 25.7 | 27.9 | .92 | 14.8 | 11.5 | 1.28 | 19.1 | 32.7 | .58 | 33.4 | 33.6 | 1.00 | 49.4 | 33.9 | 1.46 |
| South Dakota | 43.7 | 41.8 | 1.04 | 23.4 | 27.6 | .85 | 37.0 | 40.2 | .92 | 55.6 | 47.1 | 1.18 | 78.1 | 54.0 | 1.45 |
| Nebraska | 23.1 | 21.9 | 1.06 | 7.2 | 7.5 | .96 | 14.1 | 18.1 | .79 | 34.1 | 28.0 | 1.21 | 44.2 | 40.0 | 1.10 |
| Kansas | 33.8 | 29.8 | 1.13 | 4.2 | 5.3 | .79 | 21.3 | 30.2 | .71 | 50.0 | 37.5 | 1.33 | 65.8 | 45.9 | 1.43 |
| Delaware | 77.5 | 74.7 | 1.04 | 28.6 | 23.0 | 1.24 | 43.7 | 80.4 | .55 | 111.4 | 105.6 | 1.06 | 138.4 | 110.8 | 1.25 |
| Maryland* | 68.7 | 51.3 | 1.34 | 12.8 | 9.8 | 1.30 | 34.0 | 48.8 | .70 | 102.4 | 63.2 | 1.62 | 145.0 | 83.8 | 1.73 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| District of Columbia* | 76.6 | 39.6 | 1.93 | 18.9 | 15.1 | 1.24 | 34.9 | 35.6 | .98 | 100.9 | 41.7 | 2.42 | 145.6 | 60.0 | 2.42 |
| Virginia* | 54.2 | 56.2 | .96 | 11.1 | 11.1 | 1.00 | 27.7 | 41.2 | .66 | 79.0 | 65.5 | 1.20 | 160.2 | 167.9 | .96 |
| West Virginia | 56.6 | 61.1 | .92 | 13.4 | 12.5 | 1.07 | 25.6 | 46.4 | .55 | 84.3 | 85.8 | .98 | 130.7 | 134.7 | .97 |
| North Carolina* | 44.4 | 40.9 | 1.08 | 5.5 | 4.1 | 1.34 | 21.3 | 33.1 | .64 | 97.1 | 66.1 | 1.46 | 98.2 | 102.4 | .96 |
| South Carolina* | 29.1 | 30.5 | .96 | 4.2 | 4.5 | .94 | 14.6 | 26.4 | .56 | 55.8 | 48.8 | 1.14 | 82.9 | 64.8 | 1.28 |
| Georgia* | 36.5 | 35.8 | 1.02 | 5.1 | 3.5 | 1.48 | 16.7 | 25.2 | .66 | 67.6 | 54.6 | 1.24 | 98.5 | 100.4 | .98 |
| Florida* | 44.5 | 33.1 | 1.35 | 4.4 | 4.4 | 1.00 | 17.3 | 23.7 | .73 | 71.6 | 45.8 | 1.56 | 115.0 | 74.6 | 1.54 |
| Kentucky* | 74.0 | 82.0 | .95 | 19.0 | 18.6 | 1.02 | 46.4 | 68.8 | .67 | 105.2 | 103.2 | 1.02 | 200.0 | 200.0 | 1.00 |
| Tennessee* | 73.3 | 85.5 | .86 | 16.2 | 16.9 | .97 | 42.8 | 63.2 | .68 | 108.5 | 111.8 | .98 | 208.2 | 246.8 | .85 |
| Alabama* | 40.8 | 47.7 | .86 | 6.2 | 5.8 | 1.07 | 20.5 | 31.6 | .65 | 66.0 | 74.1 | .85 | 145.2 | 156.0 | .93 |
| Mississippi* | 34.2 | 36.1 | .95 | 3.6 | 2.6 | 1.38 | 11.1 | 25.8 | .43 | 63.9 | 52.0 | 1.23 | 112.0 | 113.0 | .99 |
| Arkansas* | 48.8 | 46.5 | 1.05 | 4.9 | 3.8 | 1.29 | 24.1 | 33.4 | .72 | 81.0 | 69.4 | 1.16 | 144.4 | 136.2 | 1.06 |
| Louisiana* | 58.2 | 34.5 | 1.69 | 6.2 | 6.7 | .92 | 29.0 | 29.0 | 1.00 | 103.0 | 52.4 | 1.96 | 164.3 | 75.3 | 2.17 |
| Oklahoma* | 38.8 | 36.8 | 1.05 | 5.9 | 5.8 | 1.02 | 20.0 | 30.3 | .65 | 69.9 | 52.3 | 1.33 | 108.0 | 97.3 | 1.11 |
| Texas*† | 50.3 | 52.6 | .96 | 10.3 | 9.4 | 1.09 | 32.1 | 49.0 | .65 | 99.1 | 70.3 | 1.41 | 141.0 | 105.6 | 1.34 |
| Montana | 71.2 | 35.6 | 2.00 | 24.7 | 19.7 | 1.25 | 37.4 | 37.1 | 1.01 | 96.0 | 36.0 | 2.66 | 151.3 | 61.0 | 2.50 |
| Idaho | 42.2 | 24.9 | 1.70 | 18.5 | 9.5 | 1.95 | 22.3 | 21.4 | 1.04 | 61.9 | 32.2 | 1.92 | 85.2 | 51.4 | 1.66 |
| Wyoming | 25.0 | 25.7 | .98 | 9.5 | 7.6 | 1.25 | 13.3 | 25.3 | .53 | 35.4 | 37.5 | .92 | 54.9 | 36.0 | 1.52 |
| Colorado | 120.2 | 65.3 | 1.84 | 15.1 | 13.6 | 1.11 | 62.1 | 66.6 | .94 | 224.0 | 91.6 | 2.45 | 159.3 | 81.5 | 1.95 |
| New Mexico | 159.7 | 119.2 | 1.34 | 22.2 | 26.8 | .83 | 117.8 | 137.2 | .79 | 350.5 | 184.1 | 1.91 | 209.8 | 123.5 | 1.69 |
| Arizona | 322.1 | 191.7 | 1.69 | 55.4 | 45.9 | 1.20 | 191.5 | 217.6 | .88 | 620.4 | 278.1 | 2.25 | 512.1 | 184.4 | 2.78 |
| Utah | 31.3 | 12.3 | 2.55 | 4.0 | 3.4 | 1.18 | 12.9 | 12.1 | 1.06 | 60.2 | 42.0 | 1.44 | 83.3 | 23.5 | 3.73 |
| Nevada | 122.3 | 73.9 | 1.65 | 49.3 | 51.0 | .97 | 68.4 | 97.7 | .67 | 118.1 | 47.3 | 2.50 | 309.3 | 116.0 | 2.65 |
| Washington | 62.6 | 45.8 | 1.37 | 19.3 | 18.9 | 1.02 | 43.0 | 45.7 | .94 | 78.9 | 45.2 | 1.75 | 108.7 | 55.2 | 1.96 |
| Oregon | 44.9 | 26.4 | 1.70 | 10.8 | 11.8 | .92 | 25.7 | 37.4 | .69 | 59.2 | 33.9 | 1.75 | 82.6 | 39.6 | 2.09 |
| California* | 85.6 | 50.3 | 1.70 | 18.8 | 19.1 | .98 | 40.5 | 53.9 | .75 | 117.9 | 55.7 | 2.11 | 157.6 | 58.8 | 2.68 |

* White population only.

† Rates for Texas 1933–1934.

community or State. These are multiplied when we try to explain differences for various sections of the whole country. The fact that differences have been found is not surprising when we consider the size of the United States, the variety of climatic conditions in which people live, the varying degress of concentration of population, the economic status, hygienic standards, occupations, and other environmental and social conditions in the different geographical regions. Add to these, differences in race and origin of certain population groups, sex and age of populations, dietary customs, then the problem becomes even more complex. If the human host reacts differently under different conditions, one might also expect the bacterial agent responsible for the disease to react differently. Of the latter we have no knowledge whatever.

In trying to determine what association there is between certain environmental and biological factors and tuberculosis mortality we have resorted to the use of correlation coëfficients. Although we realize that a high degree of correlation is not proof of a causal relationship we feel that when properly interpreted it is useful in determining relationships.

Certain factors which were thought to have, or have been suggested as having, some influence on the tuberculosis mortality were selected, for which we could secure fairly accurate and comparable information for all States. These were correlated with mortality rates by sex. Arizona, Colorado, New Mexico and the District of Columbia were omitted in calculating the coëfficients. The results have been tabulated in table 2 and will be discussed very briefly.

*Percentage of urban population:* Urbanization has been regarded as an important factor in producing a high mortality from tuberculosis. However, some recent reports cast doubts on such assertions. Wolff (4) reports that there is no correlation between a high percentage of urban population and a relatively high tuberculosis mortality for all classes of population (male and female combined) in various European countries. Our own studies of mortality by counties in Southeastern United States led us to the same conclusion (3).

When mortality rates are correlated with the percentage of urban population the resulting coëfficient merely suggests that high tuberculosis mortality in males is associated with a high per cent of urban population. If Southern States are not included there is a significant positive correlation $+ .66 \pm .10$. The correlation coëfficient between female mortality and urban population is not of such an order that any significance can be attached to it.

TABLE 2

*Coëfficients of correlation between tuberculosis mortality and environmental and social factors*

| | AGE GROUPS | PER CENT URBAN POPULATION | PER CENT EMPLOYED MALES IN MECHANICAL AND INDUSTRIAL OCCUPATIONS | PER CENT POPULATION ILLITERATE | PER CENT FOREIGN BORN | PER CENT COLORED POPULATION | |
|---|---|---|---|---|---|---|---|
| Males | All ages | +.40 ±.12 | +.45 ±.12 | +.31 ±.13 | +.41 ±.12 | −.14 ±.14 | |
| | 0–10 | +.23 ±.14 | | −.04 ±.14 | +.45 ±.12 | | |
| | 10–30 | +.43 ±.12 | +.43 ±.12 | +.19 ±.14 | +.54 ±.11 | | |
| | 30–55 | +.45 ±.12 | +.48 ±.11 | +.42 ±.12 | +.21 ±.14 | | |
| | 55 | +.03 ±.15 | +.08 ±.15 | +.55 ±.11 | −.12 ±.14 | | |
| | AGE GROUPS | PER CENT URBAN POPULATION | PER CENT FEMALES EMPLOYED | PER CENT POPULATION ILLITERATE | PER CENT FOREIGN BORN | PER CENT COLORED POPULATION | BIRTH RATES* |
| Females | All ages | +.09 ±.14 | +.14 ±.15 | +.49 ±.11 | −.22 ±.14 | −.13 ±.13 | −.08 ±.15 |
| | 0–10 | +.18 ±.14 | | −.15 ±.14 | +.15 ±.14 | | |
| | 10–30 | +.38 ±.13 | +.31 ±.13 | +.35 ±.13 | +.18 ±.11 | | −.37 ±.13 |
| | 30–55 | −.25 ±.14 | −.16 ±.14 | +.61 ±.09 | −.38 ±.13 | | +.34 ±.13 |
| | 55 | −.28 ±.14 | −.32 ±.12 | +.29 ±.14 | −.70 ±.07 | | +.36 ±.13 |
| | 15–44 | | | | | | −.14 ±.14 |

* Birth rate per 1,000 women 15–45 years of age.

*Occupation:* We have found in other studies (3) that a high tuberculosis mortality in the white population of certain sections of Southeastern United States is not associated with a high percentage of population engaged in industrial and mechanical occupations. In this study, when mortality rates for males were correlated with per cent of males, 10 years of age and older, engaged in industrial occupations the coëfficient is positive, $+ .45 \pm .12$. While this coëfficient cannot be regarded as a significant one, we feel that some importance may be attached to it. When Southern States are omitted from the calculations, the coëfficient of correlation becomes $+ .46 \pm .12$.

The female rate for all ages shows no correlation with per cent of females engaged in all gainful occupations. This is not surprising since the standards of living, diet, housing conditions, etc., may be much better for employed females than for many of those who remain at home.

No definite conclusions can be drawn regarding the relationship of tuberculosis mortality and per cent of persons engaged in industrial occupations. A much more refined method of treating this problem statistically has been accomplished by Miss Whitney in her contribution on *Death Rates by Occupation*, and the method should be extended and should include larger samples of population in all sections of the country.

*Illiteracy:* The coëfficient of correlation between tuberculosis mortality and per cent of illiteracy in the population is not high enough to warrant the conclusion that there is any causal relationship.

*Per cent of foreign born:* Even though the coëfficient of correlation between tuberculosis mortality in males 10 to 30 years of age and per cent of foreign born is positive we are not warranted in regarding it of much significance. For females there is still less association.

*Per cent of colored persons in the total population:* The colored population in the eastern part of the United States is principally Negro, while in the western part it is classified mainly as Indian, Mexican, Chinese and Japanese, according to the State with which we are dealing. All of these races experience much higher death rates from tuberculosis than does the white population. However, there is a negative correlation between mortality rates for either sex and the per cent of colored population. This is contrary to some opinions which have been expressed (5). Even in Southern States where Negroes make up one half or more of the population of some counties, we have not found a higher mortality among white persons.

*Birth rates:* Pregnancy has been frequently mentioned as having an

unfavorable influence on tuberculosis in females. Nicholson (6) in a study of tuberculosis mortality in young adult females of New York City came to the conclusion that pregnancy had no influence on mortality, although she stated there was evidence that it was a factor in the development of clinical evidences of the disease. Our findings in this study are in agreement with this conclusion regarding mortality. There is no correlation between mortality for females and birth rates, that is, as birth rates increase tuberculosis mortality does not consistently increase. Not even for mortality in specific age groups of females was there any correlation with the birth rate. In this study the birth rate was based on the number of births per 1,000 women 15 to 45 years of age.

## DISCUSSION OF SEX DIFFERENCES IN MORTALITY

The relatively high mortality among males in the northeastern section of the country may be the result of urbanization and industrialization of a large proportion of the population. Vermont appears to be an exception in that there is a very high tuberculosis mortality for males and a comparatively small urban population. The high rates are apparent only in the age groups 30 years and over. It is probable that the very high mortality is related to a particular industrial hazard which affects a comparatively large number of adult males, that is, silicosis. This unfavorable influence bears most heavily on males in middle and old age. In this same area the environmental factors do not appear to have had such a detrimental effect on tuberculosis mortality in females.

In many of the Rocky Mountain and Pacific Coast States the relatively high mortality among males does not appear to be the result of a concentration of the population in cities or to the fact that a large percentage of males are engaged in industrial occupations. Mortality among females in this region is comparatively low which tends to produce a high ratio for males and accounts for the relatively low rates for the total population in some of these States. In Montana for instance, tuberculosis mortality for the total population would be about as high as in Kentucky and Tennessee if the female rates were as high as the male. The same may be said of New York State!

In Midwestern and Southern States where the population is more rural than urban, female rates are about equal to or even exceed those for males. The comparatively high mortality for white males in Louisiana is due to the high rate for white males in New Orleans. Mortality in this State, exclusive of New Orleans, is about equal for males and

females. In the midwestern group both male and female rates are low except in Missouri while in several of the Southern States (Kentucky, Tennessee and Virginia) mortality for both sexes is high. In this latter group of States female rates are also equal to those for males in urban as well as rural areas, which condition does not appear to be present in the midwestern group. There is no apparent reason for the high mortality in the east central group of States.

The exceeding complexity of the whole question of sex differences in tuberculosis mortality for all sections of the United States is apparent. Our impression is that while we may generalize within certain limits with respect to the effect of specific environmental factors we are not safe in assuming that the ratio of male to female mortality will always be the same if these specific environmental conditions are found to the same degree in different sections. Our impression is that high tuberculosis death rates in different sections are probably the result of different combinations of factors.

The data do suggest, however, that, in certain areas where the rates for one sex exceed those for the other to a large degree, preventive and control measures might be concentrated to reach these specific groups. For instance, in the far Western States tuberculosis in males should receive more attention. In the northeastern section where male rates in the middle and old age groups are excessively high, the hazards of urbanization and industrialization should be studied more intensively for their possible influences on tuberculosis in males. In the South Atlantic and East South Central States tuberculosis in the older age groups of both sexes should receive more attention. Knowing more of the regional distribution of the disease and excessive mortality for special groups which appear to be particularly vulnerable to the disease, planning for control might be worked out on a more effective basis.

## SUMMARY

The principal sex differences in tuberculosis mortality when all sections of the United States are included are (*1*) the relatively high mortality rates for males as compared with females in the Northeastern and Western States, and (*2*) the relatively high rates for females in the east central section. The high rates for males are the result of high mortality in middle and old age (30 to 55 years, and 55 years and over). The high rates for females in the east central region are due in large degree to excessive mortality in old age (55 years and over).

The evidence suggests that the relatively high death rates from tuberculosis among males in the northeastern section are in some manner related to the relatively high percentage of urban and industrial population in this region. Other correlations for male and female mortality are not significant.

## REFERENCES

(1) PUTNAM, P.: Sex differences in pulmonary tuberculosis, Amer. Jour. Hyg., 1927, *7*, 663.
(2) DAUER, C. C.: Distribution of tuberculosis mortality in the white population of the United States, Pub. Health Rep., 1937, *52*, 70.
(3) DAUER, C. C., AND LUMSDEN, L. L.: The distribution of tuberculosis mortality in Southeastern United States, Amer. Rev. Tuberc., 1937, *35*, 43.
(4) WOLFF, G.: Tuberculosis mortality as an index of hygienic control, Ibid., 1936, *34*, 734.
(5) COWLES, A., 3rd, AND CHAPMAN, E. N.: A statistical study of climate in relation to pulmonary tuberculosis, Jour. Amer. Stat. Assn., 1935, *30*, 517.
(6) NICHOLSON, EDNA E.: A study of tuberculosis mortality among young women, Natl. Tuberc. Assn., Social Research Series, No. 1, 1932.

# THE INFLUENCE OF SUNLIGHT UPON EXPERIMENTAL TUBERCULOSIS[1]

A. C. UKIL AND S. R. GUHA THAKURTHA

Having noticed some striking facts, a few of which are mentioned below, which might lead us to think that open air and sunshine had perhaps played a part in influencing tuberculous infection and disease in man and animal in India and knowing that sunshine is abundant in this country, we decided to conduct some animal experiments to demonstrate the biological influence of sun-rays, if any, in this country.

We mention here some of the facts which led us to undertake this work:

(*1*) Boys and girls of the age period 6–10 years, under identical conditions, gave, at our hands (1), more or less the same frequency of positive tuberculin reaction (30 per cent). Between the ages of 11–15 years, however, when they begin to observe *Purdah* (partial seclusion at home), females show a higher incidence by 6 per cent. Between the ages of 16–20 years, the incidence in females rises to double that of males. This disparity is not noticeable in European statistics. We have not been able to think of other likely causes as a possible explanation of this disparity except that the chances of infection at home are more numerous and frequent and that the strain of adolescence might have acted differently in the two sexes.

(*2*) Cattle tuberculosis has been generally recognized as a rare disease in India. Soparkar (2) showed by inoculating both English and Indian calves of various breeds with 50 mgm. of a virulent strain of bovine tubercle bacilli that, while generalized tuberculosis was produced by this dose in English calves, a majority of the Indian calves remained clinically well and showed only minimal lesions on autopsy. Although no satisfactory reasons have been assigned for this, the relatively low susceptibility of Indian calves might have been influenced by their open air and sunshine life here.

(*3*) The results of farm experiments in Europe and India to render a herd tuberculosis-free by keeping the animals in open air and sunshine and *vice versa* are suggestive facts which stimulated our ideas.

[1] From the Tuberculosis Inquiry, Indian Research Fund Association, All-India Institute of Hygiene and Public Health, Calcutta, India.

Light therapy is now recognized as a valuable adjunct to the routine treatment, particularly of some of the extrapulmonary forms of tuberculosis. The exact mode of its action is now fairly well understood. Mayer and Dworski (3) think that healing is brought about by "a combination of successive changes, viz., hyperaemia, chemical disturbances, destruction of some bacteria and local action on the products of the existing bacteria." The direct destruction of bacilli seems to play only a minor part (4) and some think that the beneficial results are due more to the sloughing off of the tuberculous tissue (5) than to any germicidal action exercised by the ultraviolet rays. Others, such as Balderrey and Barkus (6), claim that, when the human body is exposed to direct sunlight, the alkalinity of the blood is diminished by bringing about the diminished concentration of carbon dioxide in the blood and alveoli. Rollier (7) thinks that light produces a more regular flow of blood from the depths to the surface of the body bringing about decongestion. Colebrook, Eidinow and Hill (8) showed, by exposing blood or serum mixed with tubercle bacilli and spread in a thin film to ultraviolet rays, that tubercle bacilli were not killed, that only rays shorter than 3,300 Å. showed the bactericidal effect and that the longer rays from 4,000 to 3,300 Å. proved ineffective. They also showed that the shorter rays did not penetrate the surface of the body deep enough to kill the bacilli. They think that the beneficial effect of actinotherapy is probably due to other causes, one of them being the increase of haemobactericidal power brought on by the exposure. This they showed by exposing rabbits inoculated with pyogenic cocci to sunlight, ultraviolet rays, radiant heat and certain other mildly irritant influences. They found that the augmented bactericidal power was rather transient in nature, the maximum being reached in one to two hours after which it declined rapidly to the original level. One of them (Colebrook (9)) further showed that this bactericidal activity was referable to changes in the function of the leucocytes. Hill (10) showed that the cooling effects of the air aided the beneficial action of the ultraviolet rays and that the metabolism was increased by 10 to 50 per cent. He further showed that artificial light treatment conducted in warm stagnant air indoors does not give the beneficial effect of cool air and the consequent stimulating effect on the metabolism, appetite and muscular tone. The literature on the subject is enormous. Mayer (11) has made a full review of it up to 1926.

Sunshine being abundant in the tropics, we wanted to see if it had any rôle in influencing the resistance to tuberculosis. But we did not know

the diurnal and seasonal variations of the extent and intensity of extreme ultraviolet solar radiation in this country. Hence, we were compelled to evolve an accurate method to measure it with the kind collaboration of Dr. P. N. Ghosh, Professor of Applied Physics, Calcutta University. The experiments were conducted in Calcutta and the results have been described in a previous paper (12).

The biologically active rays were found to be strongest during the months of June and July, fading rather quickly in May and the latter part of July. The ultraviolet rays were much weaker from March to May. From May to September, the intensity of the ultraviolet rays was more pronounced in the afternoon than in the morning. During the winter months, the intensity has been found to be markedly reduced in the morning. The maximum ultraviolet intensity of solar radiation was found to be between 12 noon and 2 p.m., exactly at the time when the heat rays also attain their maximum intensity. As the infrared and heat rays have been found to be distinctly harmful to inoculated guinea pigs (13), we had to face the problem of eliminating the heat rays by evolving special contrivances.

*Elimination of heat rays:* The sun's rays consist of the visible spectrum, which consists of the red and infrared zones, extending from 7,600 Å to 3,900 Å. Heat rays form more than 50 per cent of the energy of this zone. One can have ultraviolet rays from sunshine up to only 2,900 Å. If it is desired to go beyond this limit, one has to employ artificial apparatus such as quartz lamps.

The ultraviolet zone extends from 3,900 Å to 2,900 Å and beyond. This zone is made up of two subdivisions: (*1*) long rays, which extend from 3,900 Å to 3,200 Å, and which have been proved to be unimportant for biological purposes; (*2*) short rays, which extend from 3,200 Å to 2,900 Å and beyond. These are important for biological purposes.

Various devices had to be utilized in our attempt to eliminate the heat rays and to utilize the ultraviolet rays. We have filtered the sun's rays through special filter glasses. We are grateful to Dr. W. Moriköfer, Director of the Physical and Meteorological Observatory at Davos, for suggesting to us several types of filter glasses manufactured by *Deutsches Spiegel Glas A*. We tried two types of glass, (*1*) *Brephos Blau* No. 5, which allows ultraviolet rays up to 2,910 Å while cutting off nearly 90 per cent of heat rays, and (*2*) *Brephos Hellglas*, which allows ultraviolet rays up to 2,598 Å but cuts off only 50 per cent of heat rays. It may be noted that the ordinary window glass admits ultraviolet rays only up to

3,300 Å and cuts off only 5 to 10 per cent of heat rays. We are grateful to Prof. Dr. P. N. Ghosh of the University College of Science, Calcutta, for testing the filter glasses by spectrography before we began our experiments, as also after the experiments were finished. The composite spectrograph reproduced in figure 1 shows the iron arc in the centre, the new or unused *Brephos Blau* glass above and the same glass after the experiments were finished below. It will be seen that the filtering property of the exposed glass slightly deteriorated after use. The ultraviolet transmission falls rapidly from 3,100 Å.

The *Brephos Blau* glass sheets were mounted on a wooden frame, open on all sides, to support them at an angle of 30° and directed against the sun. The rear shafts of this frame were 6 feet 9 inches high and the front ones 5 feet 4 inches. A perforated platform was fixed at a height of 2 feet from the ground, covered with moist *khus khus* (a kind of grass matting), to keep off the radiated heat from the earth. The animals were kept in wire cages and placed on the platform. A draught of air

FIG. 1. Spectrograph of used and unused filter glass (Brephos Blau)

was passed through the cages by means of a table fan placed near one side of the frame. Figure 2 illustrates the arrangement introduced during the period of exposure. A thermometer was placed on the cages to record the temperature above the platform and another was tied to the front shaft of the frame in the open sun to record the temperature of direct sunlight. We adjusted the frame in such a way that the sun-rays fell at right angles to the glass surface of the filters throughout the period of exposure, as the intensity of radiation is at its maximum along normal rays and falls off as the angle of incidence increases.

## ANIMAL EXPERIMENTS

It was decided to conduct the experiments with guinea pigs. Such guinea pigs were selected for the experiment as had a minimum of black skin, as it has been shown (14) that the intensity of the penetrating active rays is twice as great for the white as for the black skins of these animals. Both shaved and unshaved guinea pigs were employed in the experi-

ments. Animals between 443 and 511 gm. in weight were employed. Exposures were usually commenced from 12 noon, as the ultraviolet rays attained their maximum strength at this time of the day. One set of experiments was done in the winter during November to January, and another set during the rainy season (August, September and October),

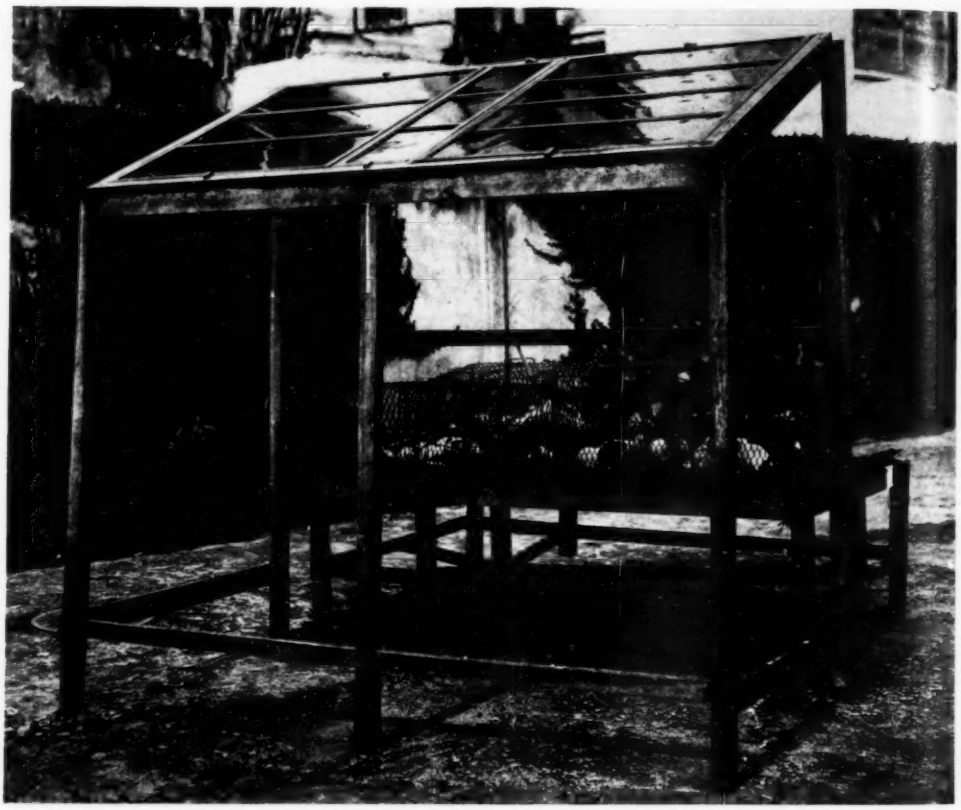


FIG. 2. Frame improvised for the exposure of animals to filtered rays of the sun

as it has been found by us that sunshine after a rain becomes much richer in ultraviolet rays.

Guinea pigs were inoculated with 0.1 mgm. of a strain (26P human type from lymph node pus) of known (mild) virulence, which was previously studied and recorded by us in a paper (15). The method of suspension and dosage has been noted in this paper. After a subcutaneous inoculation of 0.1 mgm. of this strain into the right inguinal

region, guinea pigs usually died in 52 to 78 days with a loss of weight from 20 to 155 gm. and showed the following regional incidence of lesions: right inguinal lymph node 100 per cent, left inguinal lymph node 25 per cent, pelvic lymph nodes 100 per cent, spleen 75 per cent, liver 50 per cent, tracheobronchial lymph nodes 75 per cent and lungs 50 per cent.

Colebrook, Eidinow and Hill (8) showed that the augmented bactericidal power of the blood after the ultraviolet ray exposure was reached in one to two hours and declined thereafter. We, therefore, decided to expose the animals to sunlight under various conditions not more than two hours in the day, beginning from 12 noon.

The experiments were done under four different conditions. The same number of uninoculated animals were kept in separate cages, as controls for each set of experiments, to eliminate natural infection as a cause of death. The number of the animals employed in each experiment is given in table 1.

*Experiment 1:* (Denominated later on as group 4.) One set of animals (confined in wire cages) was kept in a well ventilated room in the shade, 16 of which were inoculated and 10 uninoculated to serve as controls.

*Experiment 2:* (Denominated later on as group 2.) Another set (confined in wire cages) was exposed to direct sunlight, 16 of which were inoculated and 10 uninoculated.

*Experiment 3:* (Denominated later on as group 1.) A third set (confined in wire cages) was exposed to filtered rays of the sun under the "filter shed" described before, of which 16 were inoculated and 10 uninoculated.

*Experiment 4:* (Denominated later on as group 3.) A fourth batch of animals, consisting of 6 inoculated and an equal number of uninoculated, was kept in an open enclosure with a small shed in one corner and was allowed freedom of movement. This stimulated, to a great extent, natural conditions of free movement of the animals in open sunshine.

The problem of *dosage* in ultraviolet radiation is, at present, largely an empirical method, as the optimum dosage for a particular animal has to be found out by trial and results. Exposures were, therefore, commenced from 5 minutes and then gradually increased by 5 minutes every fourth day, until a maximum of 2 hours was reached. This was continued until the animals died or were killed. Due consideration was made for interrupted periods owing to clouds obstructing the sun's rays. The temperature variations at the place of the experiments were recorded.

TABLE 1

*Behavior of guinea pigs inoculated with tubercle bacilli on exposure to sunlight*

| | GROUP 1 EXPOSED TO FILTERED SUN-RAYS | | GROUP 2 DIRECT OR UNFILTERED SUNLIGHT, IN CAGES | | GROUP 3 EXPOSURE TO DIRECT SUNLIGHT AND SHADE WITH FREEDOM OF MOVEMENT | | GROUP 4 UNEXPOSED ANIMALS (KEPT IN ROOM) | |
|---|---|---|---|---|---|---|---|---|
| Minimum and maximum variation of temperature during the period of experiment | 23°C.–31°C. | | 26°C.–34°C. | | 24.5°C.–32.5°C. | | 21°C.–29°C. | |
| | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated |
| Number of animals used for each set of experiment | 16 | 10 | 16 | 10 | 6 | 6 | 16 | 10 |
| Average weight of animals at the time of experiment | 478.1 gm. | 419.8 gm. | 511.2 gm. | 401.1 gm. | 443.3 gm. | 468.3 gm. | 458.7 gm. | 355.6 gm. |
| Average gain (+) or loss (−) of weight when died or killed | −104.3 gm. | +12.0 gm. | −133.4 gm. | +19.5 gm. | −30.8 gm. | +37.5 gm. | −118.7 gm. | +60.9 gm. |
| Survival period of those with natural death | 54.4 days | No death | 57.6 days | No death | 85.5 days | No death | 64.0 days | No death |

The animals were weighed every week and the loss or gain in weight was recorded. Those which died within three weeks of inoculation were not counted for purposes of comparative study. In case of any doubt or early death of animals, the experiments have been repeated.

The survival period of guinea pigs exposed under different conditions as well as the number of animals employed in each experiment are depicted graphically in graphs 1, 2, 3 and 4.

A careful autopsy was done on animals which died or were killed and a search made for macroscopical tuberculous lesions at the following sites: site of inoculation (right inguinal region); right inguinal lymph node; left inguinal lymph node; pelvic lymph nodes; spleen; liver; tracheobroncheal lymph nodes and lungs. Two smears were made from the lesions at each site, stained by Ziehl-Neelsen stain and examined for tubercle bacilli, 50 fields being examined in each case before recording a negative result. In a majority of cases the macroscopical lesions showed tubercle bacilli in smears. In some cases, however, no tubercle bacilli could be demonstrated in macroscopical lesions. The size and character of the tubercles and their conglomeration in each organ were also noted.

*Variation of temperature at the time of experiment:* It was found, in the initial stages of our experiments, that the guinea pigs supported heat badly. We had to devise, therefore, various methods for lessening the effects of heat, both from sunlight from above and the radiated heat from the earth's surface below, one of which has been described above.

The minimum and maximum variations of temperature during the period of experiments were noted every day. The interposition of the filter glasses helped us to reduce the temperature by only 3 degrees from that of direct sunlight. We could not lower the temperature any further and possibly this small difference might have interfered with greatly decisive results. One chief difficulty we had to contend with was to avoid and counteract the effects of radiated heat. The room temperature was generally 1° to 1.5°C. cooler than that obtained under the filters. The temperature in a corrugated tin shed, protected from sunlight but not from radiated heat, approached that obtained under the filter shed. The maximum range of temperature variation of the atmosphere during the period of experimentation was about 8 degrees.

*Assessing the value of the experiments:* It is often difficult to assess the value of a technique in these experiments, as we do not yet possess any exact technique. But we took into consideration the following criteria: (*1*) the general health of the animals as represented by the loss or gain

TABLE 1

*Behavior of guinea pigs inoculated with tubercle bacilli on exposure to sunlight*

| | GROUP 1 EXPOSED TO FILTERED SUN-RAYS | | GROUP 2 DIRECT OR UNFILTERED SUNLIGHT, IN CAGES | | GROUP 3 EXPOSURE TO DIRECT SUNLIGHT AND SHADE WITH FREEDOM OF MOVEMENT | | GROUP 4 UNEXPOSED ANIMALS (KEPT IN ROOM) | |
|---|---|---|---|---|---|---|---|---|
| Minimum and maximum variation of temperature during the period of experiment | 23°C.–31°C. | | 26°C.–34°C. | | 24.5°C.–32.5°C. | | 21°C.–29°C. | |
| | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated |
| Number of animals used for each set of experiment | 16 | 10 | 16 | 10 | 6 | 6 | 16 | 10 |
| Average weight of animals at the time of experiment | 478.1 gm. | 419.8 gm. | 511.2 gm. | 401.1 gm. | 443.3 gm. | 468.3 gm. | 458.7 gm. | 355.6 gm. |
| Average gain (+) or loss (−) of weight when died or killed | −104.3 gm. | +12.0 gm. | −133.4 gm. | +19.5 gm. | −30.8 gm. | +37.5 gm. | −118.7 gm. | +60.9 gm. |
| Survival period of those with natural death | 54.4 days | No death | 57.6 days | No death | 85.5 days | No death | 64.0 days | No death |

The animals were weighed every week and the loss or gain in weight was recorded. Those which died within three weeks of inoculation were not counted for purposes of comparative study. In case of any doubt or early death of animals, the experiments have been repeated.

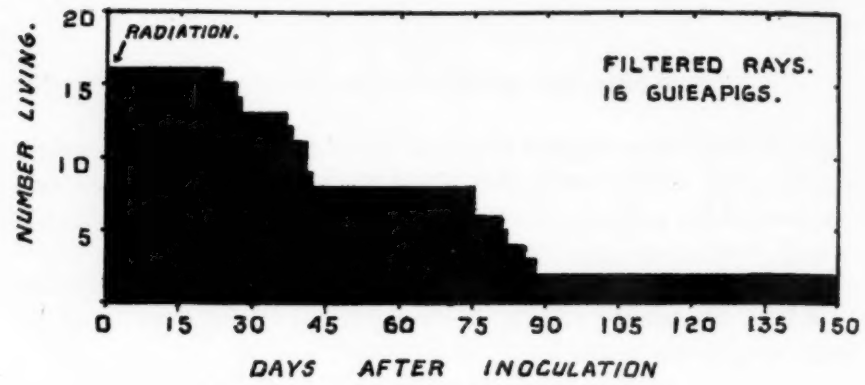
The survival period of guinea pigs exposed under different conditions as well as the number of animals employed in each experiment are depicted graphically in graphs 1, 2, 3 and 4.

A careful autopsy was done on animals which died or were killed and a search made for macroscopical tuberculous lesions at the following sites: site of inoculation (right inguinal region); right inguinal lymph node; left inguinal lymph node; pelvic lymph nodes; spleen; liver; tracheobroncheal lymph nodes and lungs. Two smears were made from the lesions at each site, stained by Ziehl-Neelsen stain and examined for tubercle bacilli, 50 fields being examined in each case before recording a negative result. In a majority of cases the macroscopical lesions showed tubercle bacilli in smears. In some cases, however, no tubercle bacilli could be demonstrated in macroscopical lesions. The size and character of the tubercles and their conglomeration in each organ were also noted.

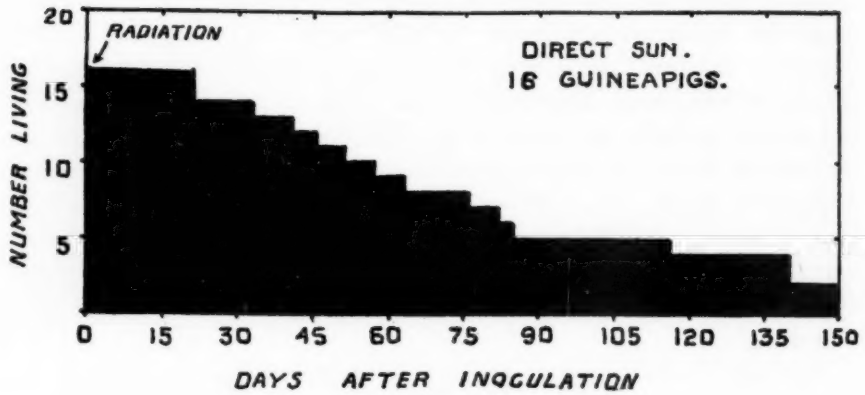
*Variation of temperature at the time of experiment:* It was found, in the initial stages of our experiments, that the guinea pigs supported heat badly. We had to devise, therefore, various methods for lessening the effects of heat, both from sunlight from above and the radiated heat from the earth's surface below, one of which has been described above.

The minimum and maximum variations of temperature during the period of experiments were noted every day. The interposition of the filter glasses helped us to reduce the temperature by only 3 degrees from that of direct sunlight. We could not lower the temperature any further and possibly this small difference might have interfered with greatly decisive results. One chief difficulty we had to contend with was to avoid and counteract the effects of radiated heat. The room temperature was generally 1° to 1.5°C. cooler than that obtained under the filters. The temperature in a corrugated tin shed, protected from sunlight but not from radiated heat, approached that obtained under the filter shed. The maximum range of temperature variation of the atmosphere during the period of experimentation was about 8 degrees.

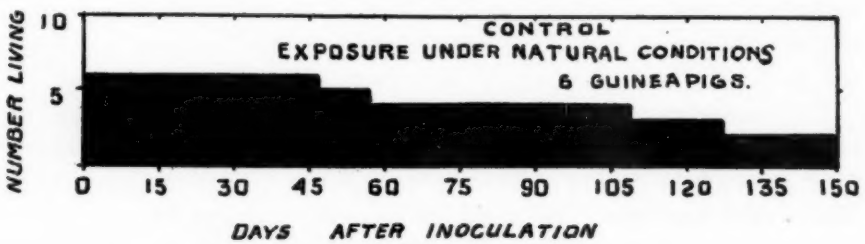
*Assessing the value of the experiments:* It is often difficult to assess the value of a technique in these experiments, as we do not yet possess any exact technique. But we took into consideration the following criteria: (*1*) the general health of the animals as represented by the loss or gain



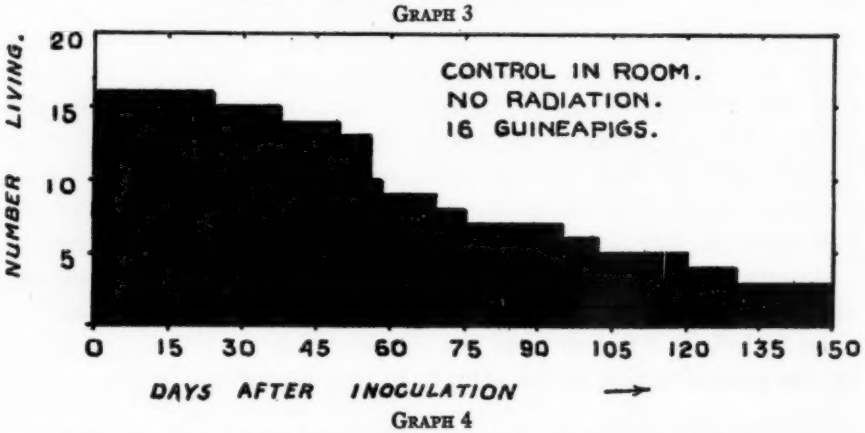

GRAPH 1




GRAPH 2




GRAPH 3




GRAPH 4

GRAPHS 1, 2, 3, & 4. Showing the survival period of inoculated guinea pigs under different methods of exposure to sunlight. The number of animals employed in each experiment is mentioned in inset.

in weight; (*2*) the survival period after inoculation; (*3*) the number and extent of the lesions found on autopsy; and (*4*) the histological appearances indicating fibrosis or healing, which is itself a difficult matter to judge in these animals.

INCIDENCE AND NATURE OF LESIONS FOUND IN THE INOCULATED ANIMALS

*Gain or loss in weight:* The uninoculated animals, which were kept under identical conditions, showed an increase of weight by 12 to 60.9

TABLE 2

*Distribution of tuberculous lesions in inoculated guinea pigs exposed to sunshine*

| SITE OF LESIONS | GROUP 1 EXPOSED TO FILTERED SUN-RAYS | | GROUP 2 EXPOSED TO DIRECT OR UNFILTERED SUNLIGHT IN CAGES | | GROUP 3 EXPOSED TO DIRECT SUNLIGHT AND SHADE WITH FREEDOM OF MOVEMENT | | GROUP 4 UNEXPOSED ANIMALS (KEPT IN ROOM) | |
|---|---|---|---|---|---|---|---|---|
| | Presence of demonstrable lesions | | | | | | | |
| | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated | Inoculated | Uninoculated |
| | *per cent* | | *per cent* | | *per cent* | | *per cent* | |
| Pus at site of inoculation | 100 | No lesion | 93.7 | No lesion | 66.6 | No lesion | 68.7 | No lesion |
| Right inguinal lymph node | 100 | No lesion | 100.0 | No lesion | 83.3 | No lesion | 100.0 | No lesion |
| Left inguinal lymph node | 25.0 | No lesion | 31.2 | No lesion | 50.0 | No lesion | 31.2 | No lesion |
| Pelvic lymph node | 75.0 | No lesion | 93.7 | No lesion | 83.3 | No lesion | 93.7 | No lesion |
| Tracheobronchial lymph node | 56.2 | No lesion | 68.7 | No lesion | 50.0 | No lesion | 56.2 | No lesion |
| Spleen | 43.7 | No lesion | 81.2 | No lesion | 83.3 | No lesion | 75.0 | No lesion |
| Liver | 37.5 | No lesion | 75.0 | No lesion | 66.6 | No lesion | 56.2 | No lesion |
| Lungs | 18.7 | No lesion | 75.0 | No lesion | 50.0 | No lesion | 50.0 | No lesion |

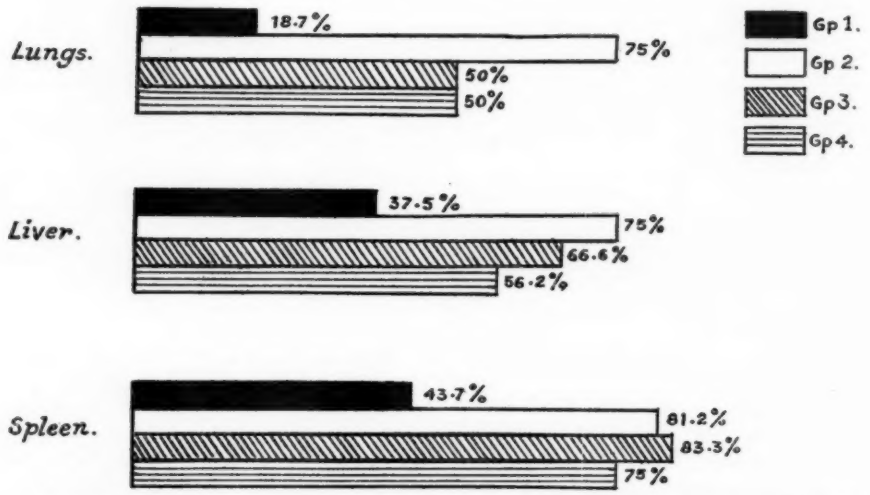
gm., whereas the inoculated animals suffered a loss in weight by 30.8 to 133 gm., before they died or were killed. Those which were kept under conditions of freedom in open air and sunshine suffered the least loss in weight and the inoculated guinea pigs in this series survived much longer than similar ones in the remaining series. The loss of weight in the other groups of experiments was more or less the same, but those exposed through filtered rays showed a lesser amount of loss (see table 1).

*Survival period:* As has been noted, the guinea pigs exposed to direct sunlight and fresh air in an enclosure under conditions of freedom sur-

vived longer than other groups (85.5 days). As regards the rest, the survival period was the lowest in the "filtered rays" group (54.4 days), the "direct sunlight" group coming next (57.6 days), while those kept in the room lived slightly longer than these two groups (64.0 days).

*Nature and distribution of lesions:* The uninoculated control animals were killed at about the same period as the inoculated ones in the same group. No lesions were found in any of the control animals.

*Average distribution of visceral lesions in the different groups.*




GRAPH 5. Gp 1 = Group 1: Exposed to filtered sun-rays, corresponding to experiment 3. Gp 2 = Group 2: Exposed to direct or unfiltered sun-rays, corresponding to experiment 2. Gp 3 = Group 3: Exposed to direct sunlight with the benefit of a shade and freedom of movement of the animals, corresponding to experiment 4. Gp 4 = Group 4: Unexposed to sunlight, that is, kept in room, corresponding to experiment 1.

The average incidence of lesions in inoculated animals is shown in table 2. The right inguinal lymph nodes showed the highest incidence of involvement, next in order were the pelvic lymph nodes, and then the spleen, liver, tracheobronchial lymph nodes in order of precedence. The percentages given in the table are average percentages.

On a glance through the comparative tables (tables 1 & 2), it will appear that the survival period of the inoculated animals exposed to filtered rays was the lowest and the dissemination of lesions much less marked in them, particularly in spleen, liver and lungs (see graph 5). It might be argued that, had the animals survived longer, they would

TABLE 3

*The time factor in the distribution of tuberculous lesions in inoculated guinea pigs exposed to sunshine*

| Period of exposure | 30 DAYS AFTER INOCULATION | | | | 60 DAYS AFTER INOCULATION | | | | 90 DAYS AFTER INOCULATION | | | | 120 DAYS AFTER INOCULATION | | | | 120–160 DAYS AFTER INOCULATION | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Experimental groups | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Number of animals inoculated | 16 | 16 | 6 | 16 | 16 | 16 | 6 | 16 | 16 | 16 | 6 | 16 | 16 | 16 | 6 | 16 | 16 | 16 | 6 | 16 |
| Number of animals died | 3 | 2 | 0 | 1 | 5 | 5 | 2 | 6 | 6 | 4 | 0 | 2 | 0 | 1 | 1 | 3 | 2 | 4 | 3 | 4 |
| | | | | | | | | | | | | | | | | | | (Killed for autopsy) | | |
| | Percentage of lesions according to site | | | | | | | | | | | | | | | | | | | |
| Pus at site of inoculation | 100 | 100 | | 100 | 100 | 100 | 100 | 100 | 100 | 75 | | 100 | | 100 | 100 | nil | 100 | 100 | 33.3 | 50 |
| Right inguinal lymph node | 100 | 100 | | 100 | 100 | 100 | 100 | 100 | 100 | 100 | | 100 | | 100 | 100 | 100 | 100 | 100 | 66.6 | 100 |
| Left inguinal lymph node | nil | 100 | | nil | 60 | 40 | 50 | 33.3 | 16.6 | nil | | 50 | | nil | 100 | 33.3 | nil | 25 | 33.3 | 25 |
| Pelvic lymph node | 66.6 | 100 | | 100 | 100 | 80 | 100 | 100 | 50 | 100 | | 100 | | 100 | 100 | 66.6 | 100 | 100 | 66.6 | 100 |
| Tracheobronchial lymph node | 66.6 | 100 | | nil | 80 | 60 | 50 | 66.6 | 50 | 100 | | 100 | | 100 | 100 | 66.6 | nil | 25 | 33.3 | 25 |
| Spleen | 33.3 | 100 | | nil | 40 | 60 | nil | 66.6 | 16.6 | 50 | | 100 | | 100 | 100 | 33.3 | nil | 50 | 33.3 | 75 |
| Liver | nil | 100 | | nil | 20 | 20 | nil | 50 | 16.6 | 75 | | 100 | | 100 | 100 | 66.6 | nil | 75 | 33.3 | 50 |
| Lungs | nil | 100 | | nil | 40 | 20 | nil | 16.6 | 16.6 | 50 | | nil | | 100 | 100 | 66.6 | nil | 25 | nil | 25 |

Group 1—Exposed to filtered sun-rays. Group 2—Exposed to direct sunlight in cages. Group 3—Exposed to direct sunlight and shade, with freedom of movement of animals. Group 4—Unexposed to sunlight or kept in room.

have shown more extensive lesions. But there were 7 animals in the group which survived from 75 to 160 days. They showed on autopsy the following incidence of lesions:

*Tubercle positive lesions*

| | |
|---|---|
| Pus at site of inoculation | 100 per cent |
| Right inguinal lymph node | 100 per cent |
| Left inguinal lymph node | nil |
| Pelvic lymph nodes | 57.1 per cent |
| Tracheobronchial lymph nodes | 28.5 per cent |
| Spleen | nil |
| Liver | nil |
| Lungs | nil |

The dissemination of lesions was the most extensive among the animals exposed to direct sunlight.

We have also tried to analyze the time factor in the distribution of the lesions in exposed guinea pigs. On an examination of table 3, it will appear that the visceral distribution in spleen, liver and lungs in animals of the "filtered rays" group becomes progressively lower until after a period of 120 days they have not showed any lesions. The animals under direct sunlight and shade with freedom of movement came next.

## HISTOLOGICAL APPEARANCES

An attempt was made to compare the histological appearances of lesions in the autopsied animals. No convincing evidence of fibrosis or retrogression could be noticed in the lesions.

*Experiments with shaved guinea pigs:* In order to see whether shaved animals behaved in a different way, we repeated the experiments with animals which were kept depilated with a depilatory made up of equal parts of barium sulphide and flour. The results of the experiments were practically identical with those carried out with unshaved animals. No difference in histological appearances of the lesions was noticed in this group. No pigmentation of the skin was noticed in these animals after exposures.

## DISCUSSION

It will be noticed that we conducted our experiments on guinea pigs of average weight and under different conditions of exposure to solar rays. One thing we were not at all satisfied about was the small difference in temperature that could be effected by interposing the filter glasses which, in the laboratory, cut off the heat rays almost entirely.

The increased temperature on the stand, therefore, must be accounted for by radiated heat from the earth's surface which, however, we tried to reduce by devising various techniques. We know that the action of the sun's rays is modified by the position of the sun in the horizon, the presence of suspended particles of dust and moisture, the amount of light reflected from the earth and the altitude. The heating of the air near the earth's surface is due more to radiation from the earth's surface than from solar radiation alone. This terrestrial radiation and convection accounted for the small difference of temperature after filtration. The choice of Calcutta, where the altitude, dust, smoke and other factors acted as handicaps, was, however, not ideal but for obvious reasons the initial experiments had to be conducted here. Although the experiments were repeated in different seasons owing to the variation in the ultraviolet content of solar radiation, there are various other factors which have to be considered in indicating facts with exactitude, for example the short-wave sky radiation, the long-wave heat radiation from the sky, the presence of clouds and the reflection of the earth's surface. The ultraviolet rays come from the skyshine, from the blue sky and white clouds as well as directly from the sun. Dorno (16) noted at Davos that the greatest ultraviolet intensity occurred on days that approached cloud formation or when the sky was lightly covered rather than perfectly clear. The diffuse daylight is relatively rich in ultraviolet rays which have such a stimulating effect on plants, animals and human beings. An increase in water vapor content of the atmosphere causes a great decrease in intensity of ultraviolet radiation. The variation in the intensity of the heat radiation is less marked than that of ultraviolet radiation according to season.

As has been shown by one of us (A. C. U.), in this country the short wave-lengths are most abundant in sunlight from noon to 2 p.m. but the high temperature of the atmosphere at this time makes it intolerable for the application of sun exposures. We have noticed the detrimental effects of heat in exposed guinea pigs repeatedly. The cooling of the atmosphere by moving fresh air is essential in stimulating metabolism and in aiding the beneficial action of ultraviolet rays. This idea prompted us to have a fan at the place of experiment.

There is considerable divergence of opinion as regards the conclusions to be drawn from animal experiments done by various workers. Mayer and Dworski (3) thought that ultraviolet rays definitely influenced the healing of corneal tubercles in rabbit's eyes. In another series of experi-

ments on the effects of radiation on guinea pigs inoculated with tuberculous sputum they found (17) that the exposed group showed very little gross tuberculosis, whereas the control group showed marked cachexia. We are not in a position to declare so boldly as regards the results of our experiments. It should not be forgotten that most of the experimenters in western countries have carried out their experiments with artificial sunlight. Apart from other considerations, the chief difficulty to be confronted in animal experiments of this nature is the elimination of heat rays and the bathing of the skin by cool fresh air. Where this happens in nature, the beneficial action of sunlight is obtained in animals. This is a matter of great difficulty in a tropical country. For therapeutic application in tuberculosis, the various other factors which influence ultraviolet radiation and which may excite excessive stimulation have to be studied as well. The facts observed by us and the excellent results obtained by Rollier in the treatment of nonpulmonary tuberculosis in the Swiss Alps call for a rational explanation and experimental proof. However, it must be admitted that convincing experimental proof is still lacking.

In trying to analyze the results of our experiments, we find that the loss of weight of animals confined in cages was higher and their survival period lower than the animals enjoying freedom of movement in fresh air. The mortality rate of animals employed in these experiments has been somewhat erratic owing to an outbreak of mortality among animals confined in cages in the animal room from an undiagnosed cause for some time. This compelled us to repeat the experiments three times. We are not, therefore, inclined to put a great stress on the survival period. If we put a greater stress on the extent and character of lesions at different periods up to and beyond 120 days, we find that the animals exposed to "filtered" rays have shown greater resistance to the evolution and extension of lesions in the viscera than the other groups. The survival period of animals which were allowed freedom of movement in fresh air and sunshine was the longest, but they showed a more extensive distribution of visceral lesions. The latter group fared better than those exposed to unfiltered sun-rays but confined in cages, probably because the intensity of the sun-rays was reduced by cool fresh air in motion.

We admit that we have employed a comparatively small number of animals for statistical purposes, although the number experimented upon required laborious examinations and controls. Perhaps, even with the

same number of animals, we would have obtained better results if the experiments were carried out in a place where the radiated heat from the earth's surface could be substantially eliminated. It appears to us that if we are to utilize the solar radiation for therapeutic purposes in this country, we must counteract the effects of heat radiation, both from above as well as from the earth's surface, as the infrared rays have been found to be distinctly injurious to tuberculous animals. In order to see whether altitude gives us any advantage or makes any difference, the experiments should be repeated somewhere in the hills in a dust-free atmosphere. The diurnal and seasonal variations must also be noted with a view to determine the most suitable hour during a particular season for preventive and therapeutic applications in man and to ascertain the optimum beneficial dosage in different clinical conditions. The most important problem will, however, be the elimination of the detrimental effect of the heat rays. Whether this will be possible by constructing solaria or by improvising tree bushes as effective filters is a matter for future study.

## REFERENCES

(1) Ukil, A. C.: The epidemiology and pathology of tuberculosis in India, I. J. M. R., 1930, *17*, no. 3.

(2) Soparkar, M. B.: The relative susceptibility of Indian milch cattle of various breeds to tuberculosis, Ibid., April, 1926, *13*.

(3) Mayer, E., and Dworski, M.: The effect of quartz-mercury-vapor irradiations (Alpine quartz-light) on experimental tuberculosis of the cornea in rabbits, Amer. Rev. Tuberc., 1924–25, *10*, 146.

(4) Eidinow, A.: The bactericidal action of light on tubercle bacilli, Brit. Med. Jour., 1927, *2*, 160.

Jansen, H.: Über Gewebssterillsation and Gewbsreaktion bei Finsens Lichtbehandlung, Beitr. z. Path. Anat. u. Allg. Path., 1907, *41*, 277.

(5) Jansen, H., and Delbanco, E.: Die histologischen Veränderungen des Lupus Vulgaris unter Finsens Lichtbehandlung, Arch. f. Derm. u. Sejph., 1907, *82*, 323.

(6) Balderrey, F. C., and Barkus, U.: The influence of light energy (sunlight) on the hydrogen ion concentration of the blood, Amer. Rev. Tuberc., 1924, *9*, 107.

(7) Rollier, A.: The therapeutic, preventive and social value of heliotherapy in surgical tuberculosis, Jour. State Med., 1928, *36*, 435.

(8) Colebrook, L., Eidinow, A., and Hill, L.: The effect of radiation on the bactericidal power of the blood, Brit. Jour. Exper. Path., 1924, *5*, 54.

(9) Colebrook, L.: The influence of sunlight upon the bactericidal power of human blood, Brit. Med. Jour., 1924, *2*, 11.

(10) Hill, L., and Campbell, J.: Metabolism of children undergoing open-air treatment, Ibid., February, 1922, 301.

Hill, L.: Sunshine and open air, Edw. Arnold & Co., London, 1924.

(11) Mayer, E.: Clinical application of sunlight and artificial radiation, Williams and Wilkins Co., Baltimore, 1926, p. 369.

(12) GHOSH, P. N., UKIL, A. C., AND SEN, M. K.: The extent and intensity of extreme ultraviolet solar radiation at Calcutta, with special reference to its therapeutic value, Proc. Indian Science Congress, Calcutta, January, 1935.
(13) LUCE-CLAUSEN, E. M., AND BAYNE-JONES, S.: The specificity of light action in experimental tuberculosis, Amer. Rev. Tuberc., 1931, *24*, 686.
(14) MAYER, E.: Clinical application of sunlight and artificial radiatin, Williams and Wilkins Co., Baltimore, 1926, p. 177.
(15) UKIL, A. C.: The rôle of secondary bacterial flora in pulmonary tuberculosis, I. J. M. R., 1930, *17*, no. 3.
(16) DORNO, C.: Der gehalt des Lichtes an Ultra-Violet, Arch. f. Opth. Berl., 1921, *104*, 170.
(17) MAYER, E., AND DWORSKI, M.: The action of quartz-mercury-vapor irradiation on inhalation tuberculosis in primarily infected and sensitized guinea pigs, Amer. Rev. Tuberc., 1924–25, *10*, 157.

# THE INCIDENCE OF EXTRAPULMONARY PRIMARY TUBERCULOSIS[1]

HENRY C. SWEANY AND WILLIAM L. M. MARTINSEN

On perusing the literature, one finds considerable differences in the reported incidence of extrapulmonary primary tuberculous infections. Lange (1) in Leipzig (1929) found 27.95 per cent extrapulmonary primaries, of which 26.80 per cent were abdominal and 1.15 per cent were in the pharyngeal region. Beitzke (2) found 4 per cent abdominal primaries in Gratz, but 15 per cent in Düsseldorf and 16 per cent in Berlin. Schürmann (3) found 11.93 per cent in Dresden; Pagel (4) 9.34 per cent in Berlin; Engel (5) 14 per cent in Dortmund; but Ghon and Winternitz (6), in a series of 606 autopsies in Prague, reported only 1.85 per cent. In America, Ophüls (7) found 6 per cent, and Klotz (8) 8.1 per cent in 477 autopsies. Of great interest is the work of Opie (9), who found 27 per cent in 66 British soldiers but none in 50 autopsies in St. Louis. One is lead to suspect that in modern communities all abdominal lesions over 10 per cent (perhaps less) are of bovine origin. One of the most important studies bearing on this question is the work of Blacklock (10) who found, in a series of 283 autopsies on tuberculous children of Glasgow, that 101 (35.7 per cent) were abdominal primary infections. In trying to arrive at an explanation of this high incidence, he cites the work of Wright who found 2.5 per cent of the milk samples of Glasgow to be contaminated with bovine bacilli, although 80 to 90 per cent of it was pasteurized. This seems to be comparable to other Scotch cities, as well as to the condition in many parts of England, as reported by Griffith (11). Blacklock found 81.8 per cent of the abdominal lesions in his series to contain bovine bacilli. By calculation it is found that bovine infections are present in 29.2 per cent, leaving only 6.5 per cent of the abdominal lesions caused by the human tubercle bacillus, a figure comparable to those of other localities where the bovine infection is better controlled.

Second in importance to the intestinal primaries is infection in the

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

pharyngeal region, principally in the tonsils. Blacklock reported 2.1 per cent cervical; Lange 1.15 per cent; and Ghon 0.54 per cent, mostly in small children. Schlittler (12) reported the clinical course of three apparently primary tuberculous infections of the pharyngeal region and cites the work of Rossner with 1.01 per cent, Worms and LeMee 3 to 5 per cent, Lundt 10 per cent, and Auffrecht 12.75 per cent. Here again there seems to be a considerable difference, but it does not seem, in this instance, that the bovine bacillus can be so much involved because Blacklock, with a high reported incidence of bovine infection, has a nominal incidence of cervical infections in his terminal cases, although a higher incidence in his surgical material. The disease here may be caused to vary more because of the mode of living, habits, etc. where there is a difference in the dosage of germs permitted to get into the mouths of the young. The report of Schürmann (13) on the Lübeck disaster is of interest in this connection where the massive doses of virulent bacilli were unintentionally given to infants as BCG. The bowel was involved in 98.3 per cent, the neck region in 78.3 per cent, the stomach and oesophagus in 18.3 per cent, and the lung in 18.3 per cent. As the dosage increases these extrapulmonary portals seem to be more frequently involved. The lesions were mostly characterized by local ulcers instead of nodules. It was, furthermore, of great interest to note that one nurse-maid testified at the trial that she held the noses of eight infants until they swallowed the germs. Of these eight, six had pulmonary primaries. This unfortunate incident, therefore, turned out to be an experiment of interest, because we see a possible cause of many lung infections by aspiration.

The other localizations of extrapulmonary primary tuberculosis are usually rare, but occasionally important. Many *bona fide* cases of primary tuberculosis of the conjunctiva are reported. Samuelson (15) cites three cases in 181,000, or about one in 60,000. Other authors report a higher incidence ranging down to one in a few thousand cases. Bergstrand (16), Blegvad (17), and others report genuine primary eye infections. There is usually the history of an ulcer on the conjunctiva with a gradual swelling of the lymph nodes at the angle of the jaw, and later an extension to the cervical lymph nodes. The tuberculin reaction has been reported to turn positive during these changes.

The internal ear is likewise mentioned, as well as the nasal cavity. Dreyfus (18) reports a case of bilateral middle ear infection that is explained by aspiration of tubercle bacilli at birth.

A more important organ is the skin, of which there are many authentic reports. Bruusgaard (19) reports ten cases in all, and laid a basis for the diagnosis of the disease. Magalhaes (20) collected 112 cases and also gives a recent and complete bibliography. Åkerberg (21) reports two genuine cases, one from a cut on the heel, the other from the socket of an extracted tooth. A great many infections are acquired through ritual circumcision, as reported by Fischel in a series of 69 collected cases, to mention only one of the most complete reports. Primary tuberculosis of the genital tract although not frequent is also possible. These uncommon localizations are important in the present work in helping to explain certain "cryptic" types of primary infections.

Besides these localizations, the pleura must be thought of as a site for primary tuberculosis. A report has been made by Courcoux and Alibert (22) outlining the clinical and biological features. We have found several calcified residues in the pleura (some in the parietal pleura) that have characteristics of primary lesions. It is admitted that such lesions must emanate from the lungs and bronchi, but some are entirely pleural and are the oldest lesions in the body.

In addition to the primary pleural foci, we have been struck by the differences between our findings and those of various other workers. We decided to analyze carefully more than a hundred cases to see whether an infection percentage of the important regions of the body could be established for this community as well as to attempt to reconcile the differences or explain the findings of other authors. Furthermore, we hope to build a standard by which we can analyze better the larger series of our autopsies.

## METHODS

In addition to a postmortem roentgenogram of the lung, the neck region in many, and all the viscera were X-rayed, and the calcifications were studied. The important ones were removed, decalcified and sectioned.

The histories of four type cases will be given to illustrate some of the principal forms. These cases are also illustrated.

*Case 1:* K. H., no. 41971 (A905), a 60 year old colored woman, was born in Arkansas and came from there to Chicago twenty-eight years before her death. She was on relief the last four years. Her past diseases included malaria at 16 years of age; a removal of her right kidney at 37; influenza at 42; radium treatments in a Chicago hospital for pulmonary cancer at 56, and

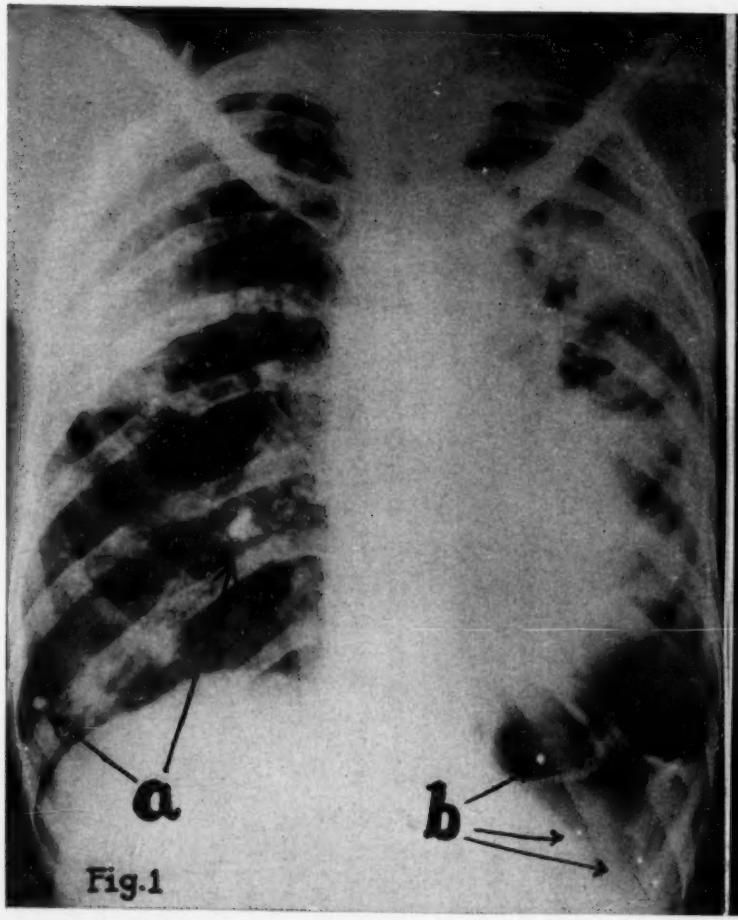


Fig. 1. Antemortem X-ray of patient K. H. (no. 41971) revealing a large primary complex in the right base (a) and in the bronchopulmonary nodes with haematogenous spread to the spleen (b).

Fig. 2. Copy of postmortem X-ray of spleen revealing the tubercles shown in fig. 1 (b).

off and on until her admission to the Municipal Tuberculosis Sanitarium on April 16, 1936. Death occurred thirteen days later.

The onset of her disease was four years before death, with cough. A roentgenogram revealed what was said to be pulmonary cancer for which she was treated with radium several times during the fall of 1932 and again in 1933, 1934 and 1935.

On admission the patient was very ill and revealed physical signs compatible with the roentgenogram shown in figure 1. The most interesting feature here is an old calcified nodular tuberculous dissemination in the spleen.

The laboratory findings revealed tubercle bacilli in the sputum, a blood sedimentation (Cutler) of 8 mm. in fifteen minutes and 14 in thirty minutes, a marked secondary anaemia, a marked polymorphonuclear leucocytosis with a moderate shift to the left. The total lymphocytic and monocytic cells were only 8 per cent.

The essential features of the pathological findings were chiefly in the lungs. There was a large primary calcification in the right border of the right lower lobe and a large mass of calcification in the bronchopulmonary nodes toward the hilum. There were also several calcifications in the left lung and some lymph node involvement toward the hilum. All of these were rather old. The whole left upper lobe was made up of a fibroid mass containing a shrunken cavity. The lower lobe was a compact atelectatic lung undergoing carnification. There was a recent tuberculous spread throughout the whole right lung, particularly in the upper lobe.

On microscopical examination, one calcified tubercle beneath the pleura had a rather dense, markedly eroded capsule, marked resorption (25 per cent), bone formation around the circumference, and lymphoid tissue replacement.

The spleen was found to contain eighteen distinct densely calcified tubercles of a great age; the right ovary contained a similar tubercle. There was no bone in either. There were a few 1 mm. ulcers in the caecum and enlarged lymph nodes of 3 cm. diameter in the mesenteric nodes.

All other findings were essentially normal or of no importance.

*Comment:* This case reveals a haematogenous spread in the spleen, probably from the large multiple primary in the lung.

*Case 2:* J. A. W., no. 42301 (A931), a 60 year old American, was born in Chicago where he lived all his life. His father died of tuberculosis one year before his own death at the age of 78 years. The patient's past diseases included a pleurisy on the right side, at the age of ten, for which he had a rib resection. He was subject to frequent colds and claimed never to have felt well. The onset was indefinite. There were no essential findings other than a far advanced pulmonary tuberculosis. The clinical findings were in keeping with the roentgenological and pathological findings.

Fig. 1. Antemortem X-ray of patient K. H. (no. 41971) revealing a large primary complex in the right base (a) and in the bronchopulmonary nodes with haematogenous spread to the spleen (b).

Fig. 2. Copy of postmortem X-ray of spleen revealing the tubercles shown in fig. 1 (b).

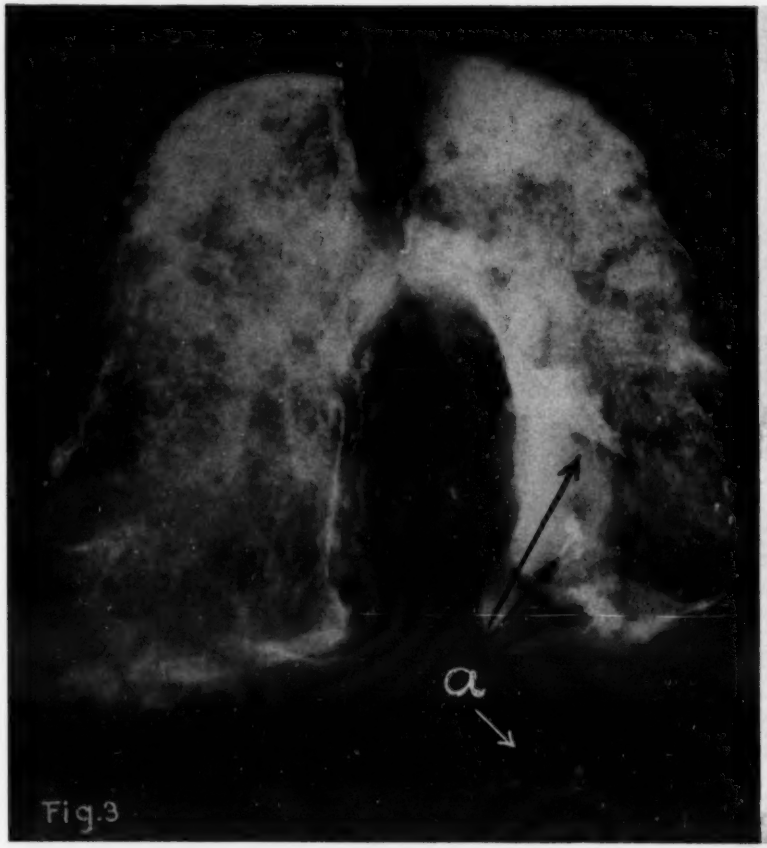


Fig. 3. Postmortem X-ray of J. W. (no. 42301) revealing only secondary calcified plaques on the left pleura at (a).
Fig. 4. Large primary in the mesenteric lymph nodes. There were no other calcifications in the body.
Fig. 5. Haematogenous foci in the spleen, probably emanating from mesenteric primary.

The laboratory findings revealed a positive sputum, a mild secondary anaemia, a mild polymorphonuclear leucocytosis with a slight shift to the left. The sedimentation was 9 and 23 mm. in fifteen and thirty minutes respectively. All else was essentially negative.

On the postmortem X-ray could be seen several calcified and perhaps ossified tubercles beneath the pleura on the left anterior margin. On section there were found very old bronchiectatic cavities in both upper lobes of a typical tuberculous nature, with blue-gray fibrous tissue around the markedly dilated bronchi; confluent acinous-nodose tubercles were present in the mid-fields within emphysematous parenchyma. At the bases was a diminishing amount of acinous-nodose tuberculosis that cleared and left a moderate amount of emphysema.

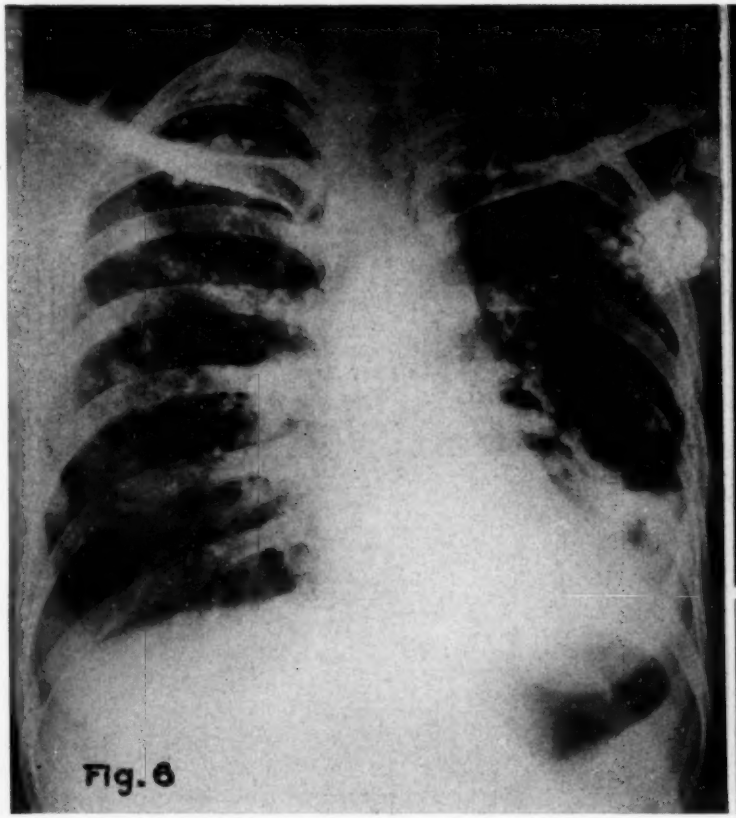
A microscopical section showed bronchiectasis with more recent tubercles in the carnified lung between the bronchi. Another one showed an old fibro-osteoid pleuritis. There was a large calcified mass in the lymph nodes of the mesentery.

Another microscopical section from a mesenteric lymph node revealed a dense calcified mass, broken up into many islands. The capsule was markedly eroded and cut, and there was fibro-osteoid tissue but no bone. There were numerous irregular nodular calcifications in the spleen from 1 to 4 mm. in diameter. They were quite "old" in microscopical appearance. There was a dense calcified centre with marked erosions between the capsule and core. The calcification had penetrated with a "water-marked" pattern about three quarters of the way to the outside of the hyaline capsule. There was an invasion of the centre at one point by fibroblasts and capillaries, but there was no bone.

Other findings revealed ulcers on the epiglottis and vocal cords, a few fresh miliary tubercles in the kidneys, two healed peptic ulcers on the pylorus, three small diverticulae in the duodenum, a small 6 mm. pedunculated polyp in the ascending colon.

*Comment:* There seems to have been a primary tuberculosis of the bowel with metastasis to the mesenteric lymph nodes and ultimately back to the lung, and then a haematogenous dissemination, as shown in the spleen.

*Case 3:* C. S., no. 41464 (A959), a 37 year old Bohemian-American, came here from Bohemia at 16 years of age. Her mother died of pneumonia (?) about thirty-three years before the patient's death. A sister of the patient died of pneumonia (?) "many years ago." She had three sisters and one brother living and well, and four brothers who were killed in the war. All her grandparents lived to be very old. She had been a nurse-maid since



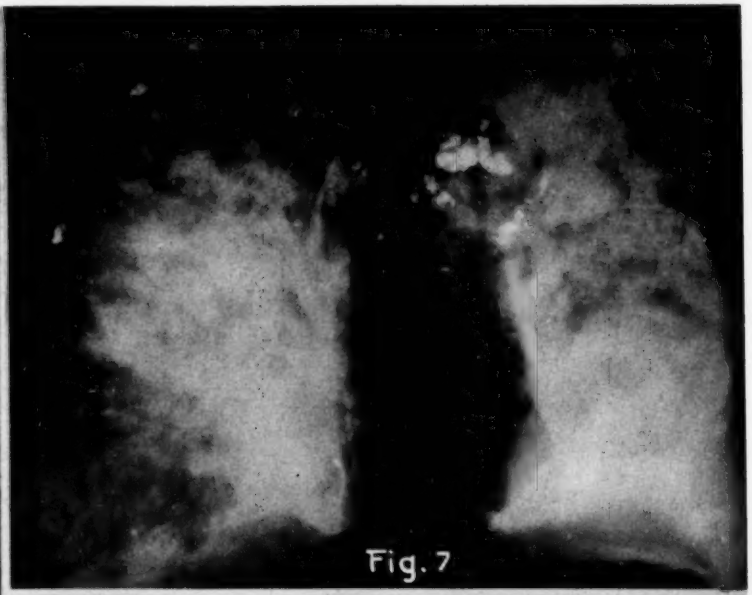



Fig. 6. Antemortem X-ray of C. S. (no. 41464) revealing a triple calcified primary. This figure reveals the calcifications in the cervical and axillary lymph nodes.

Fig. 7. Postmortem X-ray of same showing large pulmonary primary in left upper lobe and hilum with later calcifications in the right upper lobe.

Fig. 8. Calcifications in the mesentery and a large one in the peripancreatic nodes.

coming to America. The last ten years she spent caring for the children of a surgeon.

She had measles during childhood, but no other complaint until recently. She developed "rheumatism" five years before death.

The onset was with right-sided pleurisy two years before death, followed by cough, fever and tiredness. The first physician who examined her made a diagnosis of whooping-cough. He later suspected tuberculosis and sent her to the dispensary where a roentgenogram revealed tuberculosis.

Physical examination by Doctor Collins revealed a thin woman in fair general condition. The patient was lame in the right leg from "rheumatism," and there was a slight curvature of the back.

*Chest examination:* The clavicular spaces on both sides were retracted, more so on the left. There was definite dulness on the left side and a few moist râles were heard on inspiration in the upper half. On the left side the breath-sounds were diminished and many moist râles were heard throughout. Diagnosis: pulmonary tuberculosis, F. A. B., bilateral.

The roentgenogram revealed masses of calcification, the largest of which appeared in stereogram to be under the left pectoral muscles. There were also calcifications in the left axilla and left cervical nodes and many within the lung and bronchial lymphatics, as shown in the postmortem roentgenogram.

The postmortem findings in the lungs were as follows: There were a dozen or more primary-like lesions in the lung with the largest parenchymal lesion in the left apex, and calcified nodes around the left hilum and to the left of the trachea. There was a fibroid cavity in the left apex and a large cavity in the apex of the left lower lobe. The base was consolidated and was beginning to form into small cavities.

The right lung revealed several rather large calcifications beneath the pleura and smaller ones in the bronchopulmonary nodes. These tubercles appeared softer and of a younger age than those on the left side. The middle lobe was markedly contracted and contained two cavities about 3 cm. across. There was an extensive recent spread from this into the upper lobe, and the lower lobe had a dry, clearing type of process with acinous-nodose lesions extending to the pleura on all sides.

There was a huge calcification in the periportal nodes, measuring 2 x 3 cm. There were smaller calcifications in the mesenteric lymph nodes, liver and spleen. There was a large cluster of calcifications in the left cervical nodes, left axillary, and along the pectoral muscle on the left side (the latter was about 5 cm. across).

Other less important features were left adhesive pleuritis; ulcerations of the larynx and trachea; severe tuberculous ulcerations of the jejunum, ileum, caecum, colon, appendix and rectum; slight nodose goitre; brown atrophy of the liver and myocardium; and slight atheromatosis of the aorta and coronary arteries.

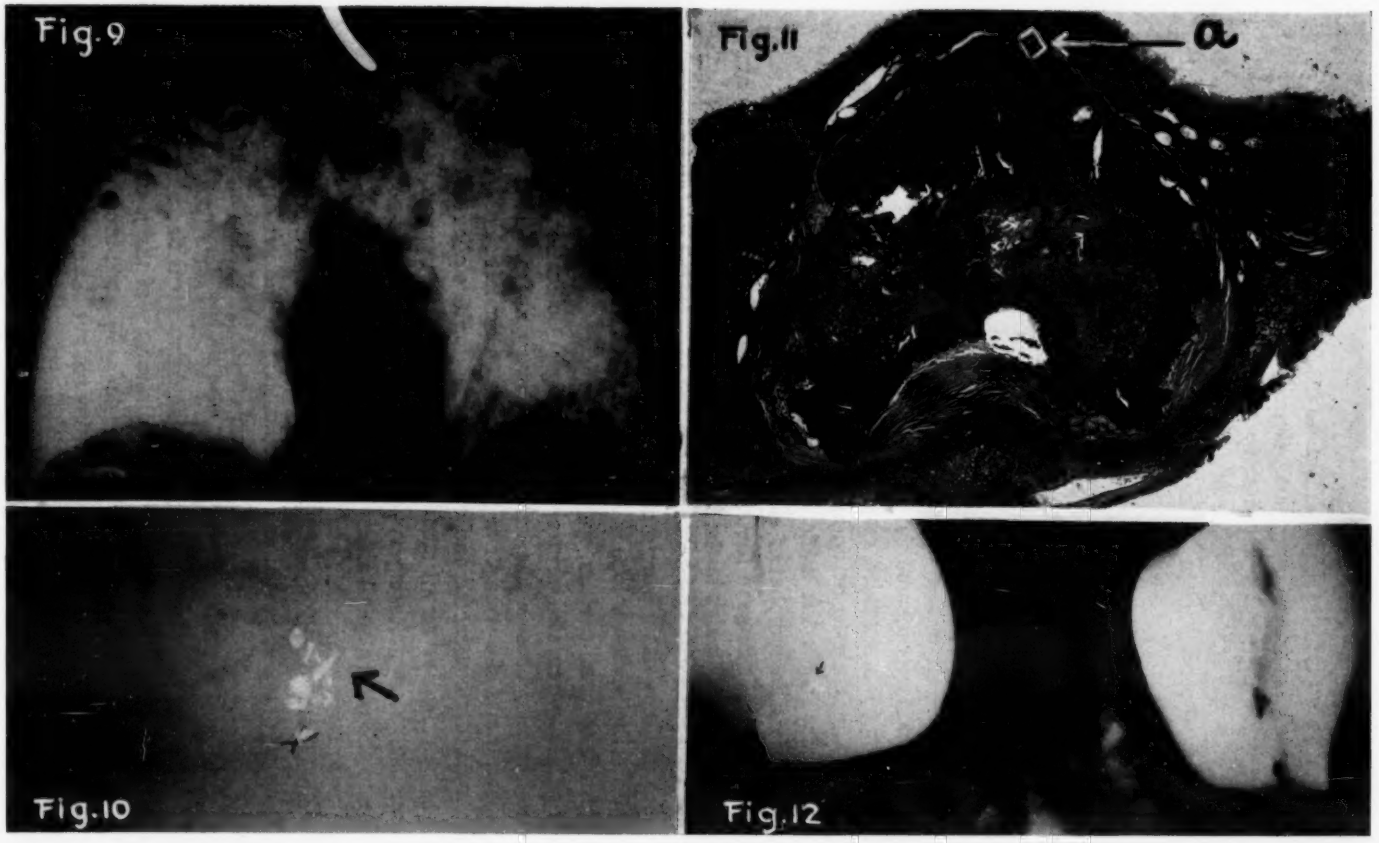



Fig. 9. A postmortem X-ray of the lung of E. C. (no. 42335) revealing no calcifications in the lung.
Fig. 10. A mass of primary calcified tubercles in the liver, the only calcified foci found in the body.
Fig. 11. A low power view of one of these tubercles. × 23, H. & E.
Fig. 12. A view of the mesentery and organs showing the tubercles in the liver.

On microscopical examination a large calcified tubercle at the left hilum revealed dense central calcification and calcification of about half the capsule. There were several deep lacunae between the capsule and the calcification with bone and marrow formation. There was a partial resorption of the capsule in places, leaving only thin reticular-like fibres. New capillaries could be seen penetrating from without. Of the many other calcified tubercles most of them revealed a character similar in most respects to the one described, but none other contained bone. Most of these were thought to be over twenty-five years of age. There were some calcifications (particularly in the right upper lobe) that were definitely of younger age, having less dense calcification, less erosion of the capsule, and showed little replacement. Still others were quite recent with very little calcification.

*Comment:* It is suggested that this patient had an overwhelming triple primary lesion twenty or more years ago, with a slowly endolymphatic and haematogenous spread until the disease became an ulcerative pulmonary process. There is a question whether her "rheumatism" was not a joint tuberculosis, although the joints were not examined.

*Case 4:* E. C., no. 42335 (A986), was a 23 year old American of Bohemian ancestry. She finished the eighth grade in school, then, for three years, she was a nurse-maid, and for four years she was a machine operator in a corset factory. There is no history of tuberculosis. She had measles, mumps and whooping-cough in childhood.

The onset was with a left-sided pleurisy three years before death. No bacilli were found in the fluid, so she was allowed to go back to work. She began to cough nine months before death, and her doctor diagnosed "bronchitis and pleural pneumonia" and gave her "electric and sun-lamp treatments." Six months before her death another doctor found tubercle bacilli in her sputum.

On admission to the Sanitarium she was too far advanced for any treatment. The physical findings were those of a far advanced "C" tuberculosis, more extensive on the right: The laboratory findings were negative except for a 10 and 26 mm. sedimentation in fifteen and thirty minutes, respectively; a marked polymorphonuclear leucocytosis with a moderate shift to the left.

The pathological findings were as follows: There were a few tiny calcifications in the wall of the oldest cavity in the right upper lobe of the lung, and no others in the body, except in the liver. The oldest fibroulcerative process was in the right upper lobe with a decreasing age all the way to the base. There was a spread to the opposite side, but it was a more typical confluent acinous-nodose type.

Fig. 12. A view of the mesentery and organs showing the tubercles in the liver.

Fig. 13. An oil immersion view along the rim of the tubercle shown at the top of fig. 11 (a). Note the transition to bone. × 1,000, H. & E.

There was amyloid in the spleen, enlarged mesenteric lymph nodes with a few caseous tubercles, a caseous tuberculous salpingitis and ulcerative endometritis. There were ulcers along the gastrointestinal tract from the jejunum to the rectum.

The postmortem roentgenogram revealed a large calcified tubercle in the liver as the only primary-like calcification in the body. One part is shown in figure 11. There was a densely calcified centre with the tissue framework still intact (note blood vessels); there was a marked encroachment of the calcification into the capsule, cutting almost through it in several places. The capsule was dense in places and was made up of a thick layer of broad banded collagenous fibres. Very early bone was present (see figure 13). The age of this tubercle is estimated around ten to twelve years.

*Comment:* This is what we have termed a "cryptic" primary. There was no local lesion found anywhere. It may have been somewhere in the head region or some other unusual portal of entry. (Figures 9, 10, 11, 12 and 13 illustrate this type.)

In table 1 the calcifications observed in 115 autopsies are listed according to number and approximate size. The latter was adjudged after the method of Opie and Anderson (23). (Figures 1, 4, 6, 7, 8 and 10.)

In table 2 are listed 7 primary lesions having two or more portals of entry (5.3 per cent). (See figures 6, 7 and 8.) In addition there were 10 other small calcifications in the mesentery that could not be definitely determined. Because of the high incidence of haematogenous spread to the spleen or liver, the possibility of a haematogenous spread must be admitted. They may also have been secondary to an earlier infection, or nonspecific, because they were too small to section and were, therefore, not comparable in age or in character to the main primary. There were seven cases in which no calcifications were found (5.3 per cent), and three (2.3 per cent) in which the calcifications were not at all typical, although the oldest lesions. These three were left in an undertermined group.

Counting all the cervical primary lesions in the 61 cases, there were four, making 6.6 per cent of all studied. There was only one localization in the cervicals alone (1.6 per cent). In order to check better this figure, 49 patients were roentgenographed routinely on entering the Sanitarium by Miss Johnson (for which we extend our sincere thanks), and only one of these revealed a definite primary calcification, 2.1 per cent. There was another doubtful lymph node involvement whose age appeared younger than a calcification in the lungs; but it may have been a double

process. There were 10 others showing enlarged nodes or slight calcifications of a questionable nature, all of which were thought to be secondary. Disregarding the one doubtful cervical process, and counting all the definite cervical primaries, it makes an average of 4.5 per cent for all, and *1.8 per cent* for primaries in the neck region alone. These would include the lymph node components of all head and neck primary in-

TABLE 1

*Localization of primary calcified tuberculous foci in 115 cases, out of a series of 132*

| | APPROXIMATE SIZE | | | | TOTAL CASES |
|---|---|---|---|---|---|
| | + | ++ | +++ | ++++ | |
| Lung | 39 | 37 | 15 | 6 | 97 (73.5%) |
| Mesentery | 4 | 1 | 2 | 4 | 11 ( 8.3%) |
| Cervical* | 0 | 0 | 1 | 0 | 1 ( 1.6%) |
| Pleura | 0 | 2 | 1 | 0 | 3 ( 2.3%) |
| "Cryptic"** | 0 | 1 | 1 | 1 | 3 ( 2.3%) |

* Based on 61 cases.

** "Cryptic" designates primary-like lesions in the liver or periportal lymph nodes without any other calcified foci in the body.

TABLE 2

*Primary tuberculosis with multiple portal of entry (7 cases out of 132)*

| | APPROXIMATE SIZE | | | | TOTAL CASES |
|---|---|---|---|---|---|
| | + | ++ | +++ | ++++ | |
| Lung and | 0 | 1 | 0 | 0 | 1 |
| Neck | 0 | 1 | 0 | 0 | |
| Lung and | 0 | 2 | 1 | 1 | 4 |
| Mesentery | 4 | 0 | 0 | 0 | |
| Lung, | 0 | 0 | 0 | 2 | 2 |
| Neck and | 0 | 0 | 0 | 2 | |
| Mesentery | 0 | 2 | 0 | 0 | |

fections in 61 cadavers and 49 living patients, most of which were of tonsillar origin.

Table 3 reveals the relation of size of the lesion to haematogenous spread. This relationship is not as close as the figures would indicate. Although the ones of one-plus size had haematogenous spread in only 15.5 per cent and all the larger sizes in over 30 per cent, there was little

difference between the two-plus and four-plus, with the three-plus showing a much higher incidence than the other two.

Table 4 reveals the incidence of haematogenous foci in the spleen and liver. The other organs were not included because in the first place such calcifications are rare, and second it is difficult to tell primary nodules in the kidney from secondary or urate kidney stones. In this series it was doubtful if there were more than two kidneys that revealed calcified haematogenous components of a primary process, although

TABLE 3

*Relation of haematogenous spread to size of lesions including all portals and the largest lesion of each (119 cases)*

| SIZE | NUMBER | HAEMATOGENOUS DISSEMINATION | PER CENT |
|---|---|---|---|
| 4+ | 13 | 5 | 37.8 |
| 3+ | 20 | 11 | 55.0 |
| 2+ | 41 | 14 | 30.5 |
| 1+ | 45 | 7 | 15.5 |
| Total | 119 | 37 | 31.1 |

TABLE 4

*Haematogenous spread in spleens and livers of all 132 cases including "cryptic" and doubtful cases*

| | | |
|---|---|---|
| Spleen alone | 14 | 10.6% |
| Liver alone | 13 | 10.0% |
| Both together | 13 | 10.0% |
| Total | 40 | 30.6% |

there were many that revealed calcifications of a nonspecific nature. As a rule, the liver lesions were fewer in number and larger than those in the spleen.

## DISCUSSION

It would perhaps be nearly correct to say that about one-third of all patients who die of progressive pulmonary tuberculosis have calcified residues of primary tubercles in the various organs, mostly in the lung, spleen and liver. So far as we can see now, it may very well apply also to all primary lesions whether they die of tuberculosis or not, providing the infection was severe enough to produce lesions of the size we have reported. What has been observed in the spleen and liver also must

occur in the bones, joints, lymph nodes, brain, adrenals, epididymes, kidney and elsewhere to a lesser degree. These various foci at one time or another no doubt form the basis of the extrapulmonary exacerbations of the disease of these various organs and tissues. All organs receive bacilli at one time or another but not many form calcifications.

Another observation from which we may profit is that in communities free from bovine bacilli the percentage of gastrointestinal primary tuberculosis may be considered to be around 10 per cent. The average given by gross pathological studies is somewhere around 6 per cent. Jaffé (24) is of the opinion that 10 per cent is the upper limit. We agree with this so far as gross findings are concerned, in *places relatively free from bovine infection*. Even so, by the use of the X-ray, lesions are found that, although small, are typical of tuberculosis and can very well cause the systemic effects of primary lesions, such as the allergic and immunological changes. With the use of the X-ray we should say that the incidence of abdominal primary infection will be found to be about 12 per cent and that any true lesions over 15 per cent are probably due to the bovine bacillus. With a more refined method of study some of the lesions now considered nonspecific may be found to be tuberculous, and thus further augment the figures of incidence.

The problem of abdominal infection seems to be largely one of dosage of the bacilli coming in contact with the mucosa. No doubt many more bacilli pass down the gastrointestinal tract than get into the lungs.

So large is the dosage in the intestinal infections that they frequently become generalized. We have found many cases in our main series where generalization resulted from an abdominal primary. A good example is shown in figures 3, 4 and 5. A comparison with generalizations in pulmonary primaries has not been made, but from our observations they are as frequent or more frequent. Pagel (4) reported two generalizations out of fourteen (15.3 per cent) cases of abdominal primary tuberculosis. Blacklock's series with a higher bovine incidence had 13.8 per cent (14 of 101 cases). There is little doubt that much smaller doses are required for the lung than for the lymph nodes of the mesentery, but the few bacilli that are inhaled or aspirated into the lungs usually grow because of a better soil in which to grow as shown by Corper and Lurie (14). Because of this the incidence of generalization from the lungs may be less in proportion than in the intestine.

A word may be said about the reason why the bovine bacilli do not affect the cervical region more frequently. The infected milk would tend to pass over the tonsils with little contact, but in the intestines

it is concentrated and absorbed so that most of the bacilli come in contact with the mucosa.

The high incidence of Blacklock's and others for surgical material need not alter this premise because the surgical specimens represent a highly selected group.

The question of aspiration as a mode of entry of tubercle bacilli has been greatly supported by the report on the eight Lübeck infants that were forcibly fed the "vaccine" of virulent bacilli. The mouth of contacts undoubtedly contains tubercle bacilli that may be aspirated by any slight choking or strangling that occurs almost daily in the life of every child. The epiglottis is only protection against large food particles under proper working conditions and not even that during a slight fit of strangling. Certainly it is not a bacterial filter.

The Lübeck work also reveals the possibilities of a multiple portal of entry, because there were only 18.3 per cent of the cases having a *single* portal of entry. This may be contrasted with Schürmann's large series from a general hospital where only 2.8 per cent had multiple primaries. If the dosage is large there seems to be every reason for bacilli to enter at several points simultaneously and each produce a typical primary complex. In our group there were seven (5.3 per cent) such cases. One may progress faster than the others and outgrow them, but in at least seven cases we felt there was justification for assuming a multiple portal of entry. It is our opinion that this figure may be actually higher because there are many smaller lesions that no doubt became extinct or were so small that we consider them "secondary" or nonspecific.

We have also pointed out the localization of primary lesions in the pleura. Some may be entirely within the pleura. If the original aspiration lodges in the last 2 mm. under the pleura, it will spread, according to Miller (25), toward the pleura. It is easily seen how such a seeding may form a lesion that projects into the pleural cavity. Contact with the parietal pleura may also transfer the lesion to the opposite wall where occasionally there will develop a larger focus than at the original site. On one occasion we have seen such a lesion on the parietal wall following a pneumothorax.

## SUMMARY

1. A study of 132 autopsies is reported in which calcified foci were studied in order to determine the percentage occurrence of each portal of entry in this community.

2. There were 73.5 per cent primary infections involving only the lungs and hilar lymph nodes. There were 79 per cent when we add the cases having multiple portals of entry.

3. There were 8.3 per cent isolated gastrointestinal infections and 12.9 per cent if we add the cases having multiple portals of entry.

4. There were 1.8 per cent isolated cervical or "head" primaries which amounts to 4.5 per cent when the cases are added having multiple portals of entry.[2]

5. There were three cases (2.3 per cent) "pleural" primaries; three cases (2.3 per cent) "cryptic" lesions in the liver or lymph nodes with no demonstrable local lesion; three doubtful cases (2.3 per cent) and seven (5.3 per cent) in which no calcifications were found. (In 71 cases no neck X-rays were made.)

6. There were 30.6 per cent of the cases showing primary haematogenous calcifications in the liver and spleen.

## REFERENCES

(1) LANGE, M.: Primary lung focus in tuberculosis in children, Ztschr. f. Tuberk., 1923, *38*, 167.

(2) BEITZKE, H.: Über primäre Intestinaltuberkulose, Virchow's Archiv. f. path. Anat., 1908, Suppl. 194, p. 225.

(3) SCHÜRMANN, P.: Ranke's primary complex in anatomical manifestations of tuberculosis, Ibid., 1926, *260*, 664.

(4) PAGEL, W.: In Henke-Lubarsch, Handbuch d. spez. path. Anat. u. Hist., vol. *3*, part 2, p. 219.

(5) ENGEL, ST.: Die Klinik des Primärkomplexes, in Engel u. Pirquet, Handb. der Kindertuberkulose, Leipzig, 1930, vol. *1*, p. 314.

(6) GHON, A., AND WINTERNITZ, F.: Zur Frage über die Häufigkeit der primären pulmonalen und extrapulmonalen Tuberkuloseinfektion beim Säugling und Kind., Ztschr. f. Tuberk., 1924, *39*, 401.

(7) OPHÜLS, W.: Some remarks on the mode of infection and of dissemination of tuberculosis in man based on anatomical investigation, Trans. Nat. Assn. Study & Prevention of Tuberculosis, 1911, *7*, 394.

(8) KLOTZ, O.: Tuberculosis in children, Pennsylvania Med. J., 1917, *20*, 811.

(9) OPIE, E. L.: First infection with tuberculosis by way of the intestinal tract, Amer. Rev. Tuberc., 1921, *4*, 641.

(10) BLACKLOCK, J. W. S.: Tuberculous disease of children, London, 1932.

(11) GRIFFITH, A. S.: The bovine tubercle bacillus in human tuberculosis, Brit. Med. J., 1932, *2*, 501.

(12) SCHLITTLER, E.: Über die Bedeutung der Tonsillen als Eintrittspforte der Tuberkulose, Schweiz. med. Wchnschr., 1934, *64*, 594.

---

[2] These figures were obtained on a different series than the main one. For this reason the total adds up to 101 per cent. Had the necks all been X-rayed, no doubt this extra one per cent would have been found among those having "no calcifications" or "doubtful."

(13) SCHÜRMANN, P.: Beobachtung bei den Lübecker Säuglingstuberkulosen, Beitr. z. Klin. d. Tuberk., 1932, *81*, 294.
(14) CORPER, H. C., AND LURIE, M. B.: The variability of localization of tuberculosis in the organs of different animals, Amer. Rev. Tuberc., 1927, *15*, 65.
(15) SAMUELSON, A.: Primary tuberculosis of conjunctiva, Nord. med. tidskr., 1936, *11*, 259.
(16) BERGSTRAND, H.: Ibid., 1929, *1*, 182.
(17) BLEGVAD, O.: Die Konjunktival-Tuberkulose, Acta Ophth., 1933, *11*, 345.
(18) DREYFUS, J. R.: Infrequent forms of infantile tuberculosis, Schweiz. med. Wchnschr., 1936, *66*, 114.
(19) BRUUSGAARD, E.: Primary tuberculous complex of the skin, Finska Läk.-sällsk. handl., 1933, *75*, 513.
(20) MAGALHAES, A. A.: Primary complex in childhood; the skin as portal of entry of tuberculosis, Prensa med. Argentina, 1936, *23*, 1600, 1643, 1700.
(21) ÅKERBERG, E.: Two cases of tuberculous primary complex of the skin, Acta dermat.-venereol., 1933, *14*, 132.
(22) COURCOUX, A., AND ALIBERT, A.: So-called primary tuberculous pleurisy and primary infection in adolescents and young adults, Paris méd., 1935, *1*, 11.
(23) OPIE, E. L., AND ANDERSON, H.: First infection with tuberculosis by way of the lungs, Amer. Rev. Tuberc., 1920, *4*, 629.
(24) JAFFÉ, R. H.: Pathology of pulmonary tuberculosis, in: Clinical Tuberculosis, ed. by B. GOLDBERG, Philadelphia, 1935, vol. *1*, pp. 97–150.
(25) MILLER, W. S.: The lung, Springfield, 1937.

# STUDIES ON THE RETROGRESSIVE CHANGES OF TUBERCLES[1]

HENRY C. SWEANY, ALMA E. TILLOTSON AND VINCENT KOZIELEK

The tubercle is one of the best known of pathological phenomena. Because it is a distinct macroscopical unit, the earlier writers were able to observe and describe it with considerable accuracy. Perhaps it was Morgagni (1) who observed it first as an entity. Later Bayle (2) and Laennec (3) described its gross appearance, the latter first recognizing the unity of all types. After the microscope was brought into use, Virchow (4), Rokitansky (5), Koester (6), Langhans (7), and Baumgarten (8), to name only a few, contributed much to the knowledge of its early evolution. Up to 1898 the literature was already quite extensive, as demonstrated by a report of Hektoen (9) in citing a review by Marchand in 1883 where there were forty-five previous publications alone on giant cells in general. After the turn of the century the accumulation continued, particularly since the introduction of vital staining methods by Sabin and her school (10); slide culture methods by Maximow and his school (11); and by the use of many other combinations of stains and culture methods by Foot (12), Miller (13), and others.

However, there is not so much known or written about the encapsulated tubercle. A "healed tubercle" to many, including perhaps some pathologists, seems to mean a nodule with a heavy fibrous wall and a caseous or calcified centre that has varying degrees of dryness and hardness. In general, the hardness is related to age, but even this is vague. Especially since the X-ray has been developed, calcified tubercles have entered into the diagnostic terminology of roentgenologists. To many of the latter group, any form of calcification of a tubercle that casts a dense X-ray shadow signifies and frequently has been called a "healed" tubercle or, equally indefinite, a "Ghon focus." This is unfortunate, for this term may be applied to tubercles of one year or fifty years of age. "Healed" rightly should only be applied to very old tubercles in which the bacilli are dead.

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

Even with complete extinction of the bacilli the changes continue in the remaining calcified derelicts consisting of encapsulated, caseous, calcified and ossified tissue. In fact, there is a constant change as the tubercle ages, apparently with the ultimate objective on the part of the body of total removal of the remnants.

So regular are some changes that they may be used, with certain restrictions, as age criteria. For instance, the early "monocytic" or epithelioid capsule develops as a general rule from about nine months to two years and then undergoes retrogression for a year or two while the fibres around the outside are forming into the heavy "specific" capsule of Aschoff (14). This "specific" capsule thickens both in depth and in the breadth of the fibres for another two to three years when it begins to disintegrate. Aschoff (14), Ranke (15), Pagel (16), Huebschmann (17), and others have described rather well this stage of tubercle formation. The maximum development of the capsule is achieved in about seven years, after which disintegration in the manner of lysis, resorption and bone formation occurs. This latter change has been studied by Beusen (18), Poscharissky (19), Puhl (20), Huebschmann (17), Mebius (21), Wurm (22), Schürmann (23), Jaffé and Levinson (24), Sweany (25), and others. The bone does not appear very early, however, in this retrogressive cycle. In hundreds of bone sections of primary tubercles studied in this institution, no bone has been observed to appear before ten years, unless there was some ground substance like the bronchial cartilages as a precursor of the bone. The bone formation and the replacement with lymphoid or marrow tissue continues to form at a rather constant rate in later life, until sometimes there is practically a complete removal of the tubercle.

To try to understand the process better and to see if we could relate the changes to any one element, we proceeded to study various tubercles in three dimensions. The method used was the well known one of William Snow Miller (26), the only deviation being the use of a heavy illustration paper instead of blotting paper. All cuts were made to scale and the reproductions are proportional to the original.

The first case studied (A642) was one having an old primary tuberculosis with a local haematogenous pulmonary seeding. There was a fibroid process in the right apex and a terminal acinous-nodose seeding. The clinical disease was of nine years' duration. The infection probably occurred about 15 to 20 years before death.

This history, while apart from the present report, gives a background that is useful in interpreting the findings.

Model 1 was taken from the old haematogenous seeding and corresponds with tubercles ordinarily rated at twelve to fifteen years old. As a general rule all the tubercles of this haematogenous seeding were of this same age character. There appears first a lysis of the outer border of the calcified area next to the heavy fibrous capsule, then small end capillaries begin to appear in these lacunae; later they ramify into a vascular network, the opening enlarges and the borders begin to take on a bluish-pink stain on section. The nuclei of the fibrocytes become stellate. Still later lymphoid cells appear around the capillaries. Sometimes yellow bone-marrow cells may be seen.

It was noticed that two rather constant elements were present in this process of disintragation; first, there were usually many pigmented

---

PLATE 1

Fig. A642-1. Photograph of a reconstruction of a small segment of a calcified parenchymal tubercle of Autopsy 642, showing an early type of disintegration by capillary invasion. × 113

Fig. A642-2. A more advanced stage of disintegration of a tubercle of a hilar lymph node, showing larger capillaries. × 53.2

Fig. A589. A photograph of a top view of a bony tubercle of Autopsy 589, showing a shell of bone with large capillaries penetrating from each end. × 28

---

phagocytes in the vicinity of these changes, and, second, there was a bed of capillaries somewhere outside the capsule. Occasionally neither have been observed, but this is not the rule.

The sections reproduced show the various levels as they are marked on the model. There is little evidence of lymphoid and marrow tissue at this stage.

Model 2 is from a hilar lymph node of the same case, which reveals a more advanced stage of resorption with a more extensive capillary bed, although even here they still seem to be end capillaries. There is a large amount of free pigment as well as some in phagocytes. There is a well advanced replacement with lymphoid tissue.

Accompanying the capillary invasion in this specimen are large numbers of fibroblasts. The entire significance of these is not yet clear nor is their relation to the capillaries. At times they seem to precede the capillaries, while at other times they may not be present at all. In some rare specimens they seem to behave as a special form of phagocyte to engulf calcified material after which they appear first as a myxomatous tissue, then as cells resembling osteoblasts which later form bone. In

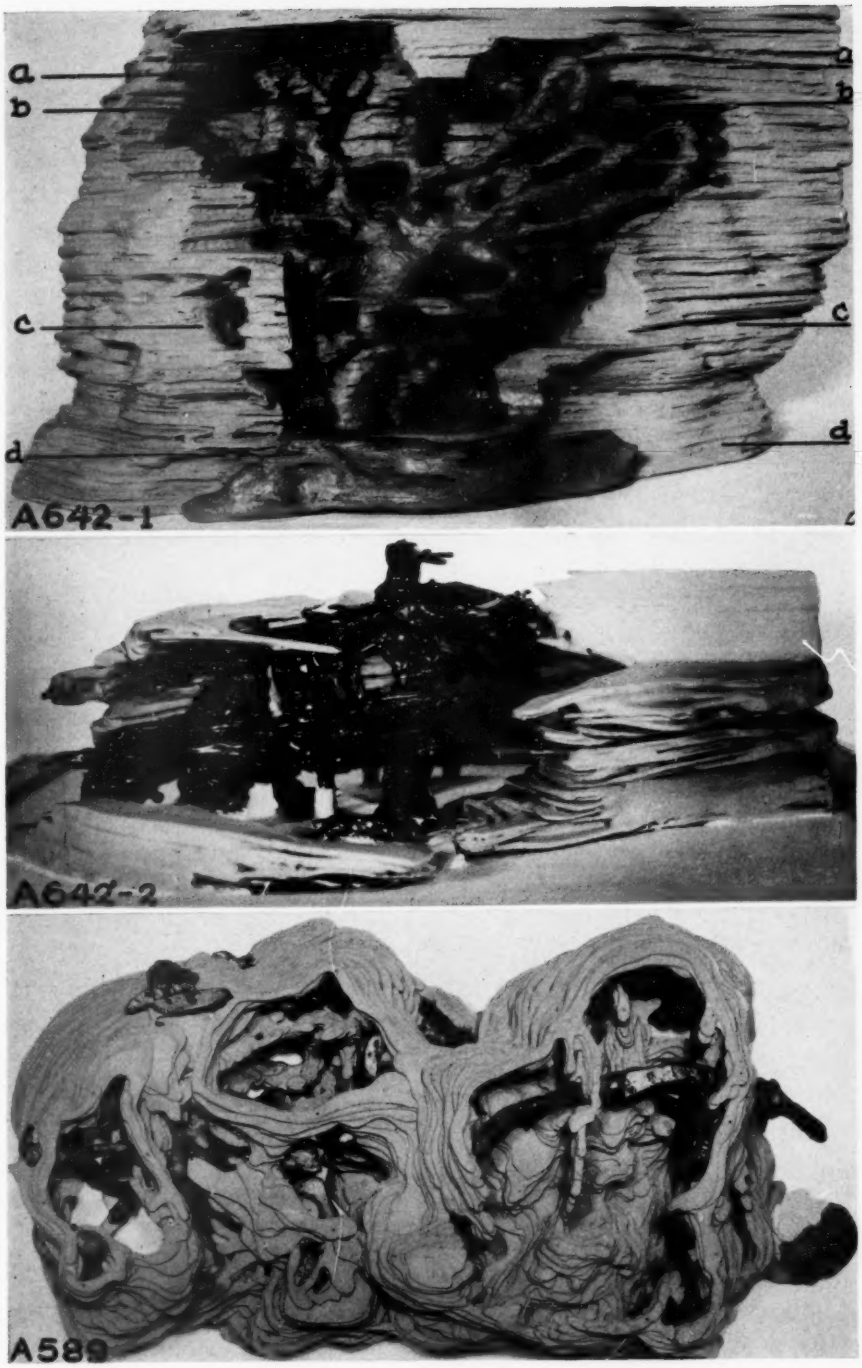



PLATE 1

the slide culture studies of Maximow (27), Lang (28), and Bloom (29) the apparent changes from one cell type to another vary so widely in different circumstances that it would be hazardous to predict the possible origin and evolution of such cells.

Model 3 is from a case (A589) infected from the patient's mother at two and one-half years of age, and dying at the age of 51, with intermittent clinical disease during all his life. The probable age of this tubercle is over 40 years, and perhaps nearer 50 years.

There is almost a complete resorption of the calcification and capsule with a replacement by bone and lymphoid tissue and a small amount of yellow marrow. The main blood vessel here has taken on more the character of an arteriole and passes through the tubercle, joining the capillary bed on the opposite end of the tubercle. The new capillaries seem to be more like a ramified plexus of arteriolar capillaries rather than an arteriole-venule junction.

---

PLATE 2

Fig. a. Photograph of a microscopical section taken at a top level, marked "a" in fig. A642-1, plate 1, showing capillaries in the centre of erosions and a plate of bone on the outside. × 149

Figs. b & c. Photographs of lower levels, marked "b" and "c" in fig. A642-1, plate 1. × 149

Fig. d. A photograph at the point of entrance of the main capillary. × 149

---

The new capillaries have apparently formed much in the manner they do in wound healing.

Not all tubercles show a complete resorption. In tubercles that have formed with a minimum of caseation there is a myxomatous-appearing ground substance left that is perhaps a residue of the original fibrous or elastic tissue. This framework affords a support for the new vessels and lymphoid and marrow tissue. Furthermore, only about half of the calcified tubercles contain bone, even though the other changes take place.

## DISCUSSION

The evolution of the tubercle is a phenomenon that brings into play practically all the factors of defense against disease that the animal organism possesses. In the discussion we shall deal only with the healing tubercle. This has been done before and at length by Aschoff (14), Puhl (20), Huebschmann (17), Ranke (15), Pagel (16), Jaffé and Levinson (24), and others. Following the acute and early toxic action, the subacute foreign body action of the bacillary wax and the dead

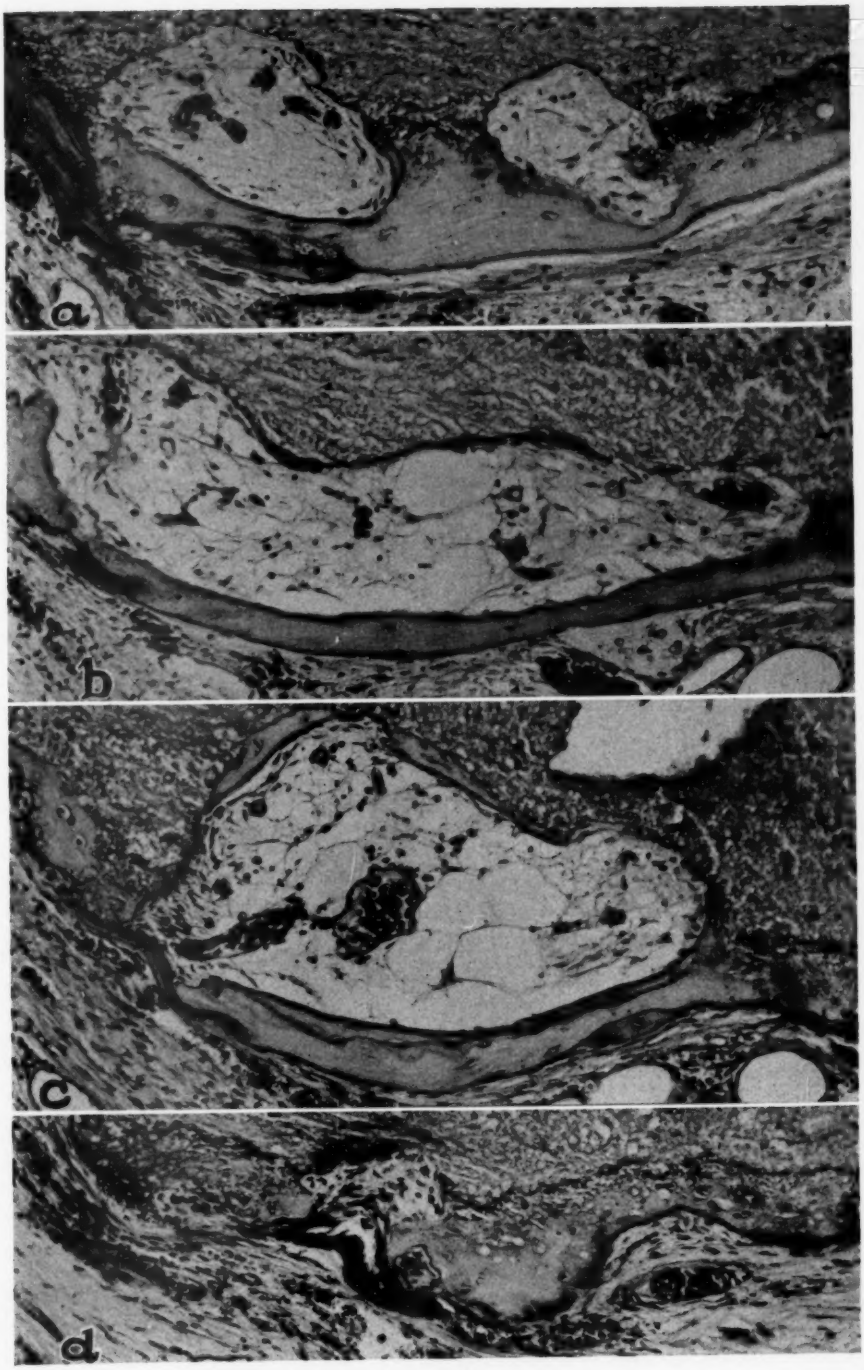



PLATE 2

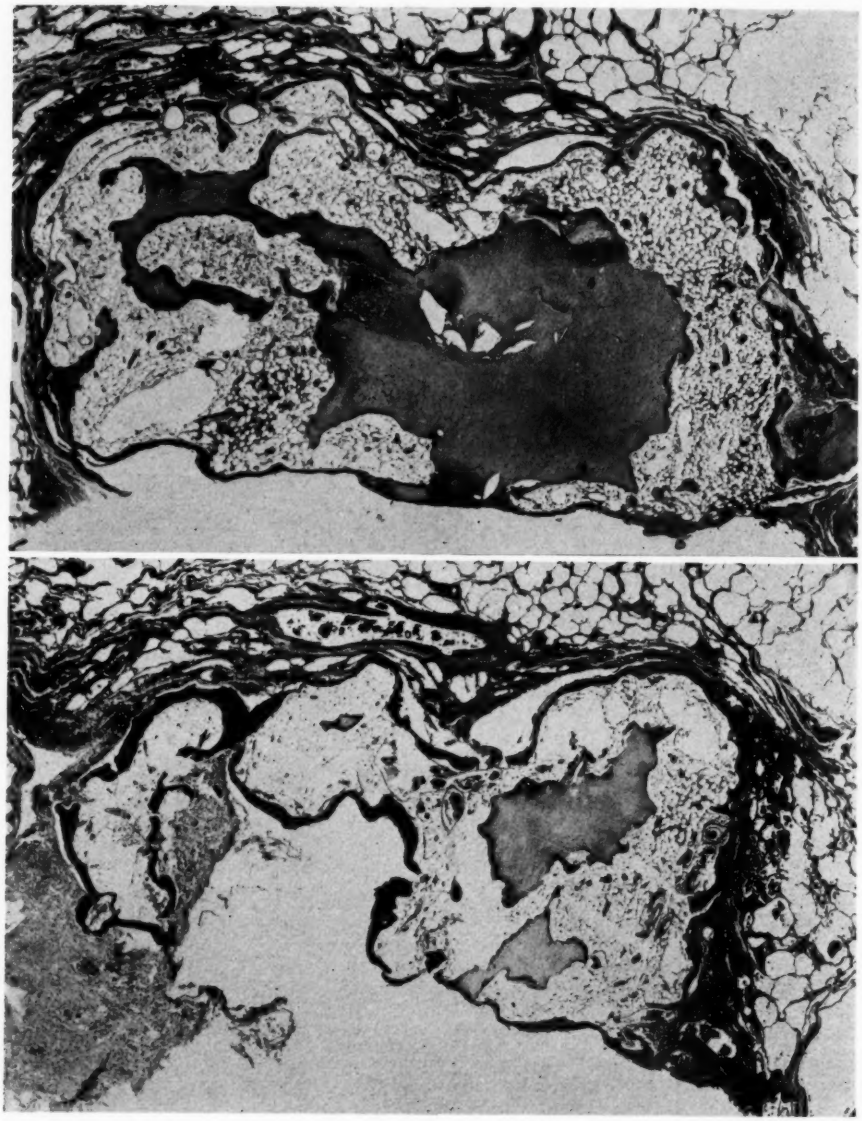


PLATE 3

Top figure. Photomicrograph of a section through the centre of a tubercle of Autopsy 589, showing resorption, capillaries, early lymphoid tissue and shells of bone encroaching on the calcified centre. × 12.6

Bottom figure. The same near the top of the model. × 12.6

tissue caseum causes the stimulation of fixed tissue cells and chronic granulation tissue, forming a firm capsule. As the debris ages there is a gradual transformation of the dead tissue into elements of a lower molecular weight. This autolysis of the central core probably liberates many acid radicals that become combined with calcium ions either already present or diffusing in from the body fluids. The process of calcification continues outward to meet the capsule which it finally penetrates, wave upon wave, (resembling Liesegang rings) each new ring perhaps depending upon the further production of free acid ions within. As these waves of calcification roll outward toward the periphery, the pericapsular lymph and blood capillaries seem to supply autolyzing enzymes that open up spaces between the old connective tissue fibres and then follow in with new endothelial cells to form an arborization of capillaries. Although Huebschmann (17) has called attention to the fact that tubercles may be attached to an arterial pedicle, it seems that it is not so much the larger vessels that count as the finer capillaries adjoining the outside of the capsule. The autolysis continues, more capillaries form, and the bordering fibrous tissue is transformed into a purple-pink staining ground substance with the nuclei of old fibrocytes gradually appearing like bone cells. Although the heavy "specific" capsule is largely if not completely avascular, the fine capillaries weave their way between the crevices of fibrocytes until they may reach far into the centre of the tubercle. This penetration is assisted by a movement of the calcification outward. Perhaps it is a mutual process.

In the large number of tubercles we have studied, we have not seen bone form on the *inner* border of the capsule *unless* capillaries were in the vicinity. We are of the opinion that most retrogressive changes taking place in tubercles are largely a function of their proximity to the circulating fluids and tissues, particularly the blood capillaries. The tubercles, therefore, that are not accessible to these factors, as those in advanced emphysematous areas, or collapsed lungs due to disease or pneumothorax, will not change at the same rate as those surrounded by a rich capillary bed. In addition, there are certain very old tubercles that do not form bone, although hyalinization and connective tissue ingrowths occur. These are usually lacking in capillary beds around the outside, but there are notable exceptions.

The lack of osseous changes in such cases cannot be explained from our present data, but they are perhaps related to deep seated characteristics of the host that concern calcium metabolism and the multipotentiality of fibroblasts. Fibroblasts in the spleen also seem to lack the property

to form bone. In many sections of spleen we have never seen any bone but have found it occasionally in the liver and mesenteric nodes. There must be a different type of fibroblast, therefore, in the spleen than elsewhere in the body, as conditions for bone development are different in this organ.

On the other hand, it has been observed that the bronchial cartilages form bone much earlier than the connective tissue capsules around the tubercles. It seems to be much easier for cartilage to become transformed into bone; whether it is due to the closer relationship of the cartilage cell to bone or to the presence of utilizable calcium is problematical. In one specimen I observed a ring of bone around the border of a bronchial cartilage with true red marrow within. Mebius (21) has reported this actually in a tubercle and not in ossified cartilage. There is every reason to believe from our studies as well as those of Leriche and Policard (30), Jaffé and Levinson (24) and others, that in certain cases the fibrous tissue around calcified caseous tubercles becomes supersaturated with calcium and transformed into osteoblasts by indirect metaplasia. No doubt all pathological calcifications are subject to the same changes. Irrespective of the type, it is apparently due more to a certain relationship of ions and living tissues in abnormal environment than to any purposeful process.

## SUMMARY AND CONCLUSIONS

A three-dimension study of old primary tubercles seems to point to the facts that the changes taking place in the aging of tubercles are dependent upon several factors: first, the autolysis or enzymatic digestion of tissues that have been killed; the calcification of this digest; and then the proximity of these elements to the circulating fluids of the body which permits of resorption and ossification. The capillaries around the outside of the tubercle seem to penetrate the capsule and, either through a deposition of phagocytes or a liberation of enzymes between the calcification and capsule, cause a lysis of the old fibrocytes and calcareous material. The capillaries then enter the lacuna that is produced and become ramified within. Simultaneously fibroblasts enter and become transformed into fibro-osteoid and bone tissue that lines the walls of these spaces. This process apparently continues until the remnants of calcified caseum and perhaps even bone tissue are removed. On rare occasions fibroblasts seem to enter independently of capillaries and act to dissolve the calcium; but more study must be given this phenomenon before anything can be said of it.

## REFERENCES


(1) MORGAGNI, G. B.: De sedibus et causis morborum, 1761.

(2) BAYLE, G. L.: Recherches sur la phthisie pulmonaire, Paris, 1810.

(3) LAENNEC, R. T. H.: De l'auscultation médiate ou traité du diagnostic des maladies des poumons et du coeur, Paris, 1819.

(4) VIRCHOW, R.: Die krankhaften Geschwülste, Berlin, 1865.

(5) ROKITANSKY, C.: Hanbuch der pathologischen Anatomie, 1855, Band 1, 295.

(6) KOESTER, K.: Über fungöse Gelenkentzündung, Virchow's Archiv, 1869, *48*, 95.

(7) LANGHANS, T.: Über Riesenzellen mit wandständigen Kernen in Tuberkeln und die fibröse Form des Tuberkels, Ibid., 1868, *42*, 382.

(8) BAUMGARTEN, P.: Über Tuberkel und Tuberkulose, Berlin, 1885.

(9) HEKTOEN, L.: The fate of the giant cells in healing tuberculous tissue as observed in a case of healing tuberculous meningitis, Jour. Exper. Med., 1898, *3*, 21.

(10) SABIN, F.: Studies of living human blood cells, Bull. Johns Hopkins Hosp., 1923, *34*, 277.

(11) MAXIMOW, A. A.: Tuberculosis of mammalian tissue in vitro, Jour. Inf. Dis., 1924, *34*, 549.

(12) FOOT, N. C.: The endothelium in experimental pulmonary tuberculosis, Jour. Exper. Med., 1920, *32*, 533.

(13) MILLER, W. S.: Reticulum of lung; its presence in reparation process of tuberculous lesion with and without caseation, Amer. Jour. Path., 1927, *3*, 217.

(14) ASCHOFF, L.: Über die natürlichen Heilungsvorgänge bei der Lungenphthise, 1922.

(15) RANKE, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, Berlin, 1928.

(16) PAGEL, W.: Die allgemeinen pathomorphologischen Grundlagen der Tuberkulose, Berlin, 1927.

(17) HUEBSCHMANN, P.: Pathologische Anatomie der Tuberkulose, Berlin, 1928.

(18) BEUSEN, W.: Inaugural Dissertation, Göttingen, 1898.

(19) POSCHARISSKY, J. F.: Über heteroplastische Knochenbildung, Beitr. z. path. Anat., 1905, *38*, 135.

(20) PUHL, H.: Über phthisische Primär-und-Reinfektion in der Lunge, Beitr. z. Klin. d. Tuberk., 1922, *52*, 116.

(21) MEBIUS, J.: Über die formale Genese der heterotopen pericalcären Knochenbildung, Virchow's Archiv, 1925, *255*, 416.

(22) WURM, H.: Über Spätveränderungen an alten tuberkulösen Primär-Komplexherden und Reinfekten, Beitr. z. path. Anat., 1926, *75*, 399.

(23) SCHÜRMANN, P.: Der Primärkomplex Rankes, Virchow's Archiv, 1926, *260*, 664.

(24) JAFFÉ, R. H., AND LEVINSON, S. A.: Histological studies on healed tuberculous primary lesions of the lung, Amer. Rev. Tuberc., 1929, *20*, 214.

(25) SWEANY, H. C.: Studies on the pathogenesis of primary tuberculous infection. I. The regressive lesion, Ibid., 1933, *27*, 559.

(26) MILLER, W. S.: A description of plastic models (reconstructions) of a conglomerate tubercle and the surrounding structures in a human lung, Ibid., 1919, *3*, 65.

(27) MAXIMOW, A. A.: Cultures of mammalian blood leucocytes. From lymphocyte to monocyte to connective tissue, Arch. f. exper. Zellforsch., 1928, *5*, 169.

(28) LANG, F. J.: Reaction of lung tissue to tuberculous infection in vitro, Jour. Inf. Dis., 1925, *37*, 430.

(29) BLOOM, W.: Mammalian lymph in tissue culture. From lymphocyte to fibroblast, Arch. f. exper. Zellforsch., 1928, *5*, 269.

(30) LERICHE, R., AND POLICARD, A.: The normal and pathological physiology of bone, English translation by MOORE, S., AND KEY, J. A., 1928.

# TUBERCULOUS DISSEMINATION DURING THERAPEUTIC PNEUMOTHORAX[1]

## A Study of Three Cases

WILLIAM A. ZAVOD

In the last two years I have had an opportunity to study three cases of pulmonary tuberculosis that were complicated by tuberculous dissemination while under treatment with therapeutic pneumothorax. The spread was apparent in the noncollapsed lung, but the extent of involvement of the collapsed lung was a matter of conjecture, since the lung under treatment in each case was either completely or nearly completely collapsed and neither the roentgenograms nor the physical examination could offer a solution. The three cases came to postmortem examination soon after the complication and thus offered an opportunity to investigate some of the debated questions, such as: (*1*) Can bronchogenic or haematogenous spread occur in a completely or partially collapsed lung? (*2*) Do various grades of atelectasis and ischaemia in a compressed lung influence the extent of spread of disease in that lung? Because the number of cases is so small conclusive answers are not to be expected and deductions therefore are made on this basis.

That a collapsed lung can be spared in a generalized miliary tuberculosis has been known for several decades. Forlanini (1) reported such a case in 1909. Lindblom (2) in a postmortem study of 15 cases of pulmonary tuberculosis that were treated with pneumothorax stressed the absence of miliary tubercles in the collapsed lung of one of his cases while the other lung and the abdominal viscera showed extensive miliary tuberculosis. Case 15 in his report showed a similar phenomenon, though he did not emphasize it.

The literature, though inconclusive, is fairly rich in experimental investigation of the problems raised in this paper and others closely related. Most of the work was done in order to determine how does collapse of a diseased lung influence the healing of tuberculosis. The

[1] From the Department of Pathology, Dr. Gilbert Dalldorf Chief of Laboratories, and the Department of Tuberculosis, Dr. John M. Nicklas Chief Clinician, Grasslands Hospital, Valhalla, New York.

conclusions that the different investigators have reached are very diverse and the disagreement is due to the difference in experimental approach (Pinner (3)).

Summarizing the literature we find that two schools exist, one that is of the opinion that hyperaemia follows the collapse of a lung (Sauerbruch, Lindblom, Photakis and others), and the other, a larger school, that believes that various grades of ischaemia are the resultants of collapse of a lung (Forlanini, Brauer, Rolland, Roubier, Gardner, Coryllos and others). My personal experience after postmortem study of 51 cases that have had pneumothorax for a period from several months to four years convinced me that in general the extent of interference with the circulation and ventilation in a collapsed lung is directly proportional to the extent of collapse. Some cases show hyperaemia in the early phases of collapse which is due to greater compression of the pulmonary vein than the pulmonary artery.

Investigation of the problems of tuberculous dissemination during the course of therapeutic pneumothorax involves ventilation in bronchogenic dissemination and the state of the vascular tree in haematogenous spread, since these are the respective avenues of invasion.

*The collapsed lung and bronchogenic dissemination:* Accepting the descriptions of the microscopical anatomy of the acinus of the human lung offered by Miller, Husten, Laguesse, Seemann, and Grethmann, which differ from one another to some extent, we learn that the acinus is the terminal unit of the pulmonary parenchyma. It is composed of one type of nonciliated respiratory epithelium and is the usual seat of bronchogenic dissemination. Aschoff (4) believes that the transition from ciliated epithelium, still present in the first divisions of the interlobular bronchioles, to respiratory epithelium in the acini and the slowing of the air current favor the settling of foreign bodies and microörganisms in the acinus. When we examine a collapsed lung we find that its air content is markedly reduced; gross section shows that the organ is more or less solid, the normal pattern of the lung is no longer visible. Microscopically the alveoli and smaller bronchioles are compressed and the acini have lost their identity. Only the larger bronchioles lined with ciliated epithelium remain patent though somewhat compressed.

The normal physiology of respiration is markedly altered in a collapsed lung. As has been repeatedly noted on fluoroscopy a completely collapsed lung under positive pressure does not expand on inspiration. The respiratory excursions of a collapsed lung under negative pressure

are limited in most cases. In those cases of therapeutic pneumothorax that were complicated by a tuberculous effusion, the thickened visceral pleura prevents respiratory movement of that lung whether the intrapleural pressure is negative (before refill) or positive (after refill).

To illustrate the rôle played by the above anatomical and physiological changes in a collapsed lung during a bronchogenic dissemination the following case is presented.

*Case 1:* M. D., 23 year old white girl, was admitted January 1, 1935 complaining of dry cough. Family and past histories were negative. The onset of the present illness was in October, 1934 with cold and cough. After several weeks treatment with no relief, a roentgenogram was taken which showed an exudative tuberculous process about 2 cm. in diameter in the left upper lobe. There was no evidence of cavitation; the right lung was clear. The sputum was negative on concentration and guinea-pig inoculation. She was at rest in bed until July, 1935 when a roentgenogram showed a sudden increase in the infiltration about the original focus. The sputum remained negative, Therapeutic pneumothorax on the left was instituted on July 26, 1935, a free pleural space was found and an effective collapse resulted. She gained weight and was discharged on May 28, 1936 as arrested; the sputum was never positive. Refills were continued in the outpatient clinic. The intrapleural pressures were near zero on the negative side. About the middle of September, 1936 she had sudden fever of 101°F. and malaise for one week. A roentgenogram taken at that time showed no change and the episode remained unexplained. She had no expectoration, the left lung was nearly completely collapsed, the right lung was clear, refills were continued in the clinic. During December, 1936 she began to expectorate and tubercle bacilli were found on direct smear. Though the fluoroscopic examination showed no change in her condition she was readmitted. A roentgenogram taken on January 11, 1937 (figure 1A) showed no change. The temperature was normal. On the next day, January 12, she had sudden fever of 103°F. with chills and sweats, the fever gradually rising to 105°F. A roentgenogram taken on January 21, 1937 showed a pneumonic consolidation at the base of the right upper lobe; the left lung was collapsed and showed no apparent change (figure 1B). Therapeutic pneumothorax on the right was started on January 21; the pleural space was free. The left lung was permitted to reexpand passively, refills having been discontinued. The fever remained high; slowly increasing dyspnoea developed that was ascribed to the bilateral pneumothorax; her condition was not considered alarming. On the night of February 10, 1937 she had a sudden attack of severe dyspnoea and was dead when the physician on call arrived only a few minutes after the onset of the episode. Death was pronounced due to asphyxia, and rupture of the right lung with a tension pneumothorax suspected.

Fig. 1A

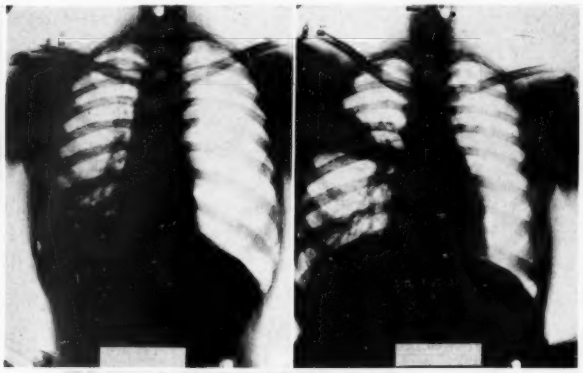


Fig. 1B

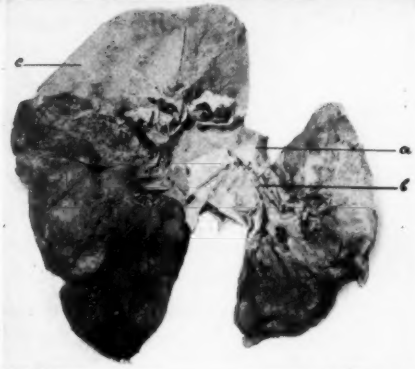
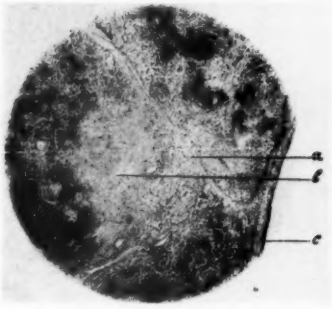



Fig. 1C

Fig. 1D



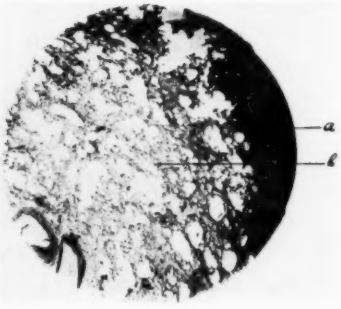




Fig. 1E

*Case 1*

Fig. 1A. Roentgenogram January 11, 1937. Complete collapse of left lung, right lung clear.

Fig. 1B. Roentgenogram January 21, 1937. Slight reëxpansion of left lung, pneumonic consolidation at base of right upper lobe.

Fig. 1C. Sagittal section through both lungs. Left lung collapsed. Caseous tissue on left lateral wall of trachea (a). Caseation and ulceration of left main bronchus (b). Caseous pneumonia in right upper lobe (c). No evidence of tuberculous pneumonia on left.

Fig. 1D. Microscopical picture of section of the right pneumonic lung. Interlobular septum (a). Caseous tissue (b). Exudative elements in alveoli (c). × 10

Fig. 1E. Microscopical picture of left lung. Thick pleura (a). Partly collapsed alveoli with thickened alveolar walls (b). No evidence of recent tuberculous pneumonia. × 10

Autopsy excerpts: Upon removing the sternum without puncture of the pleural cavities, the heart was found slightly displaced to the right. Incision into the right pleural cavity showed no evidence of air under pressure or spontaneous collapse of the lung. The right pleural cavity was free throughout; the right lung was about 20 per cent collapsed; there were no adhesions; about 50 cc. of clear serous fluid was present. The left lung was about 70 per cent collapsed; a large band adhesion extended from the collapsed upper lobe toward the apex and several string adhesions were seen posteriorly extending into the gutter of the spine.

Gross section of the lungs revealed: Right lung: the visceral pleura was smooth, glistening and showed no pathological change. The interlobar septum between the upper and middle lobes showed recent adhesion that could be separated with ease. The entire upper lobe showed dense pneumonic infiltration with beginning caseation; there was no evidence of liquefaction or cavity formation (figure 1C). The middle and lower lobes were partly collapsed; acinous-nodose infiltration was seen in the middle lobe and upper portion of the lower lobe. The left lung was the size of a large spleen; the visceral pleura was covered with a thin coat of fibrin that could be scraped away. The upper half of this lung was fairly solid, the lower half was slightly crepitant. Section disclosed dense infiltration in the upper half of the upper lobe undergoing fibroid change, the lower lobe was free of tuberculous involvement and partly reëxpanded. Dissection of the trachea and bronchi showed a cauliflower mass of caseous and granulation tissue in the left main bronchus about 1 cm. below the bifurcation that narrowed the lumen of the bronchus to a few millimetres in diameter. The trachea was much smaller than normal, measuring only 15 mm. in diameter; the mass of caseous tissue extended from the left bronchus into the lumen of the trachea occluding it completely but not adherent to the tracheal mucosa. Upon scraping the caseous tissue away a deep ulcer was found in the posterior inferior wall of the left bronchus. Further dissection disclosed that the ulcer extended into a caseous bronchial node situated between the two main bronchi and densely adherent to the left bronchus (figure 1C). The remaining nodes in that region were all caseous, some of them undergoing softening and liquefaction.

Microscopical examination: Sections of the right upper pneumonic lobe showed markedly thickened interlobular septa, the lobules were densely infiltrated with caseous tissue (figure 1D). Individual caseous areas that showed tendency to become confluent were seen in some lobules while others showed beginning breaking down in the centre of the caseous tissue. Examination under higher power showed that the centres of many caseous areas were free of cellular elements and few lymphocytes and polymorphonuclear cells were seen at the periphery. No giant cells were found. Slight perivascular and peribronchial thickening was apparent. Elastica-stain showed

the elastic fibres still intact in many caseous areas imparting the appearance of a honeycomb. Sections from the middle and lower lobes showed an occasional caseous nodule with exudative reaction around it. Sections from the left upper lobe showed marked fibrous thickening of the pleura. Some alveoli were partly or completely collapsed, others showed emphysematous distention (figure 1E). The alveolar walls were thickened; many areas had hyalinization with round cell infiltration and giant cells. Sections from the lower lobe showed partial collapse of the alveoli, the sections were free of tuberculous involvement. Sections through the left bronchus and its adherent lymph node showed destruction of all bronchial structures and extension of the caseous tissue from the lymph node into the bronchus. Sections through other intrathoracic lymph nodes showed complete caseation void of cellular elements or giant cells. All other organs and systems were free of tuberculous involvement grossly and microscopically.

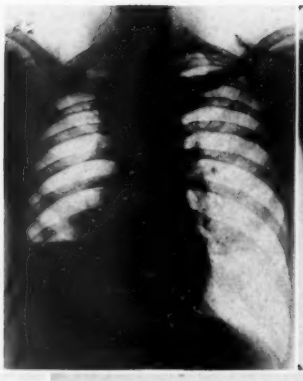
*Comment:* Apparently the caseous lymph node at the floor of the bifurcation ulcerated into the left bronchus in December, 1936 when the sputum became positive for tubercle bacilli. The dissemination to the right lung did not occur until January 12, 1937 (roentgenogram January 11, 1937 was negative and there was no fever) when the temperature suddenly rose to 103°F. The ulceration in the left bronchus must, by that time, have become extensive enough to liberate caseous tissue rich in tubercle bacilli. The collapsed lung on the left was free of new involvement in spite of the fact that the ulceration was in the bronchus on the same side. This was probably due to the collapse of the left lung for the following anatomical and physiological factors: (*1*) the acini which are the usual seats of bronchogenic spread were collapsed by therapeutic pneumothorax at the time the spread occurred; (*2*) the larger bronchioles which remained uncollapsed are lined with ciliated epithelium and, should the products of tuberculous disease be carried into their lumina, the cilia will carry them back toward the trachea before they have had a chance to become implanted; (*3*) a collapsed lung of long standing expands very little during respiration and therefore no strong air currents are created that would facilitate dissemination.

*The collapsed lung and haematogenous dissemination:* Accepting the hypothesis that the ischaemia created in a collapsed lung is in direct proportion to the extent of collapse, the completely collapsed lung will correspondingly have greater ischaemia and probably very limited communication between the arterial and venous pulmonary circulation which normally takes place through the capillary bed only. Given

a bacillaemia in the venous circulation of the greater circle the microorganisms will be carried to the right heart and then to the lungs by way of the pulmonary arteries. The microörganisms ordinarily lodge in some of the capillaries and begin to grow. The capillary network like the pulmonary acinus creates an environment favorable to the implantation of the tubercle bacillus because the circulation is markedly slowed, there is a greater supply of oxygen from the nearby alveoli, and the size of the capillaries is such that they will easily hold back clumps of tubercle bacilli. When the capillary bed is collapsed the microörganisms may not have a foothold or a favorable environment to begin growth. With these hypotheses in mind the following two cases are presented for illustration.

*Case 2:* S. S., a 45 year old Negro man, was admitted to the hospital on July 20, 1933 complaining of pain on swallowing, cough and expectoration. In his early childhood he was in close contact with his tuberculous mother, otherwise the family and past histories were negative. The onset of his present illness was in January, 1933 with cold and pain in the chest. Pleurisy and subsequently tuberculosis was diagnosed. A roentgenogram on admission showed a productive process in the upper half of each lung suggestive of haematogenous tuberculosis. Two cavities were seen in the right upper half with a total diameter of 7 cm., and one 3 cm. cavity in the left upper half. The epiglottis was ulcerated, the cords were normal, the sputum was scant but positive for tubercle bacilli. Therapeutic pneumothorax was started in July, 1933; a free pleural space was found, a satisfactory collapse resulted, the cavities in the collapsed lung were not definitely seen on the roentgenogram and were considered closed. The cavity on the left closed on bed-rest; the sputum, however, remained positive and the ulcerated epiglottis was considered the offender. A hot effusion (tuberculous effusion with fever) on the right appeared in November, 1934 and the pleural pressures became positive after a refill of 100 to 200 cc. of air. The fluid remained serous though cloudy in later months. His course was uneventful. A roentgenogram in October, 1936 (figure 2A) showed no change in the patient's condition when compared with films taken two years back. Examination of the epiglottis showed that the disease was progressive. The epiglottis was by this time completely destroyed and the cords became ulcerated, swallowing was painful. On December 26, 1936 his temperature rose to 101°F. and the patient was dyspnoeic. A roentgenogram taken the same day showed haematogenous dissemination over the entire left lung, the right remained unchanged (figure 2B). The dyspnoea was progressive; the fever stayed at the same level; there was no clinical evidence of involvement of any other organ; the spinal

Fig. 2A



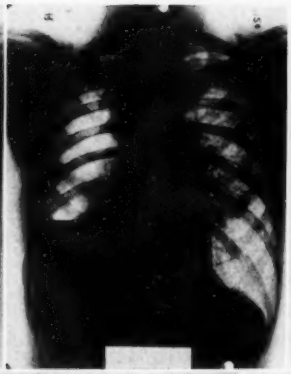


Fig. 2B

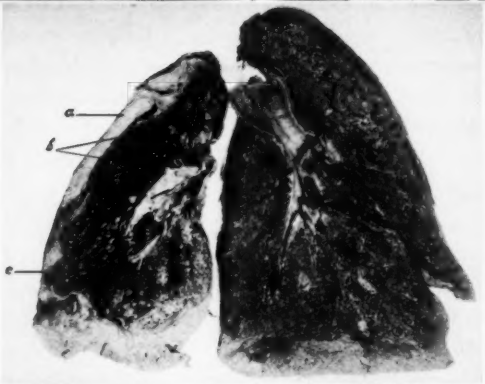
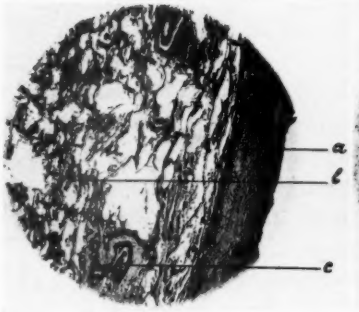



Fig. 2C

Fig. 2D



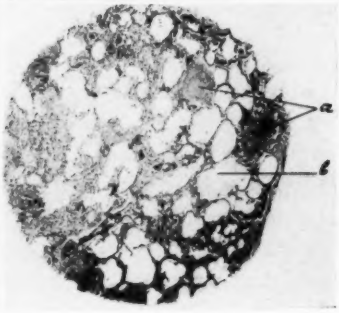




Fig. 2E

*Case 2*

Fig. 2A. Roentgenogram October 16, 1936. Complete collapse of upper two-thirds of right lung, partial collapse of lower third. Effusion on right. Very fine diffuse fibrosis and emphysema over entire left.

Fig. 2B. Roentgenogram December 26, 1936. No apparent change on right. Very fine miliary dissemination throughout left, more dense in upper two-thirds.

Fig. 2C. Sagittal section through both lungs. Complete collapse of upper and middle lobes (b). Parietal pleura (a). Partly collapsed lower lobe with miliary tubercles (c). Dense miliary dissemination over entire left. Emphysema left.

Fig. 2D. Microscopical picture of section of base of right upper lobe. Very thick pleura (a). Collapsed alveoli with thickened walls (b). Compressed large blood vessels (c). No miliary tubercles found. × 10

Fig. 2E. Microscopical picture of section of base of left upper lobe. Many recent miliary tubercles (a). Distended alveoli (b). × 10

fluid was normal; the sputum remained scanty and positive for tubercle bacilli. Respirations became gradually more difficult and he expired on February 1, 1937.

Autopsy excerpts: Upon removing the sternum, the right pleural cavity was found to be filled with about 300 cc. of cloudy fluid. The parietal and visceral pleurae were covered with a thick shaggy coat of fibrin. The upper and middle lobes were completely collapsed and pushed into the vertebral gutter. There was a thick cord-like adhesion extending from the upper lobe to the second rib posteriorly. The lower lobe was partly collapsed. Dissection from the right main bronchus into the bronchial tree disclosed that the upper lobe bronchus led into a cavity, 6 cm. in diameter, that was flattened by the anteroposterior collapse of that lobe by pneumothorax. The cavity walls were thick, covered with a pyogenic membrane and purulent sanguineous exudate. The middle-lobe bronchus opened into a 2 cm. cavity in the middle lobe. The cavities showed no tendency to become obliterated in spite of the fact that the upper and middle lobes were collapsed for three and one-half years. The remaining parenchyma in these two lobes was collapsed and showed discrete nodular deposits infiltrated with calcium. No recent tubercles were seen. The right lower lobe was partly collapsed, congested with blood and sparcely infiltrated with recent miliary tubercles. Between the tubercles, fine sponge-like emphysema was seen (figure 2C). The left lung had no adhesions, it was voluminous, congested, heavy yet crepitant throughout and distended with air. The visceral pleura was dull and studded with very fine grayish tubercles. The interlobar septum showed recent adhesions. Section of the left lung showed dense infiltration with miliary tubercles from apex to base with coarser nodules in the upper half. The parenchyma between the tubercles was distended with air. The blood vessels were congested giving the tissues a deep purple color. A scar was found at the base of the upper lobe in the position where a cavity was seen in the original roentgenogram on admission.

Microscopical examination: Sections from the right upper and middle lobes showed no miliary tubercles. The visceral pleura was fibrous and many times the normal thickness. The walls of the alveoli were thickened, some alveoli were completely collapsed and others were distended and had broken walls (figure 2D). The blood vessels and bronchioles were collapsed and showed marked perivascular and peribronchial thickening. Several caseous areas with hyalinized centres were encountered. Sections from the lower lobe showed many recent miliary tubercles with giant cells and caseous centres. Other tubercles appeared to be older with definite capsules and hyalinized centres. Sections from the left lung showed very slight thickening of the pleura due to a cellular exudate. Miliary tubercles were abundant subpleurally and in the parenchyma. The alveoli were distended (figure 2E).

The tubercles appeared to be recent with giant cells at the periphery, mononuclear cells and caseous centres; other tubercles had a well formed capsule, homogeneously filled with inspissated caseous tissue and free of cellular elements.

The spleen and kidneys showed an occasional tubercle grossly and microscopically. A few small shallow ulcerations were found in the ileum near the ileocaecal valve. The prostate was caseous throughout, with beginning liquefaction.

*Case 3:* L. V., 44 year old white man, a hard-coal miner for over 20 years, was admitted to the hospital in 1932 complaining of loss of weight. The onset of his symptoms was at the end of 1931 when pulmonary tuberculosis was diagnosed. Roentgenograms at the time of admission showed a tuberculous process involving the upper third of the right lung and the upper two-thirds of the left lung with cavitation in the latter. He expectorated about 20 cc. of mucopurulent sputum that was positive for tubercle bacilli on direct smear. A diagnosis of pulmonary tuberculosis, probably of haematogenous origin, and pneumonoconiosis was made. Therapeutic pneumothorax on the left side was started in August, 1932. An effective collapse resulted, the cavity closed and his sputum became negative in April, 1933. He was discharged in November, 1933 and refills were continued in the outpatient department. In December, 1934, three weeks following the last refill, he was brought to the clinic complaining of slight fever, headache and dizziness. Fluoroscopic examination showed a haematogenous dissemination over the entire right lung and he was readmitted to the hospital. A roentgenogram taken at the time of admission showed complete collapse of the left lung and a very fine miliary seeding throughout the right (figure 3B) that was not so evident on a previous film (figure 3A). Symptoms of meningeal involvement became pronounced, the spinal fluid contained tubercle bacilli, and a diagnosis of miliary tuberculosis with tuberculous meningitis was made. The sputum remained negative. The course was progressively down-hill and he expired nine days following admission.

Auptosy excerpts: Upon lifting the sternum, the right lung filled the right hemithorax and did not collapse. The right pleural space was free and the lung had no adhesions. The left lung was completely collapsed and crowded against the spinal column. The left pleural space was free of fluid and contained three fibrin bodies. The parietal and visceral pleurae were covered with a hoary fibrin deposit. The right lung was voluminous and distended with air; many fine tubercles were seen through the visceral pleura. Gross section revealed miliary tubercles densely infiltrating the lung from apex to base, the dissemination being most marked in the upper two-thirds. The parenchyma between the tubercles showed emphysematous distention. The

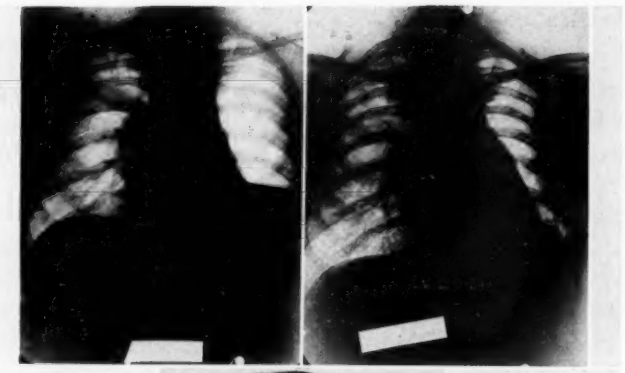


Fig. 3A

Fig. 3B

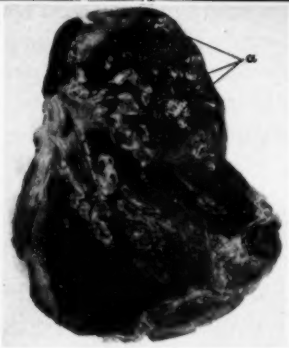



Fig. 3C

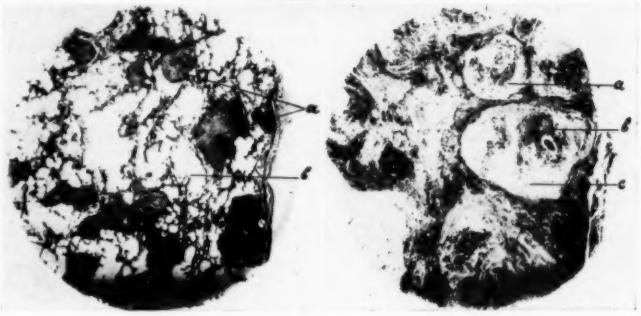



Fig. 3D

Fig. 3E

*Case 3*

Fig. 3A. Roentgenogram June 4, 1934. Complete collapse of left lung with effusion. Nodular infiltration throughout the right.

Fig. 3B. Roentgenogram December 3, 1934. Left lung shows no important change. Right lung shows very fine miliary dissemination throughout.

Fig. 3C. Sagittal section through left lung. (Unfortunately the right lung was not preserved.) Complete collapse of left lung. Inspissated caseous tissue (a). No miliary tubercles seen.

Fig. 3D. Microscopical picture of section of right lung. Many recent tubercles (a). Distended alveoli (b). × 10

Fig. 3E. Microscopical section of left lung. Complete collapse with marked fibrosis. Silicotic nodules (a). Centre densely infiltrated with carbon (b). Hyalinized tissue (c). No evidence of recent miliary tubercles. × 10

left lung was collapsed to the size of a large spleen and extremely hard. On section this lung was black. Several areas of inspissated caseous tissue were seen in the upper half and fine calcific deposits in the lower half. The two lobes were densely adherent and the interlobar septum was thick. There was no evidence of miliary tubercles and no cavities were seen (figure 3C).

Microscopical examination: Sections from the right lung showed slight thickening of the visceral pleura. Many recent tubercles with caseous centres and giant cells were seen subpleurally and in the parenchyma. The vesicles between the tubercles were distended, some of the septa were broken. The blood vessels and bronchioles were thickened (figure 3D). Sections from the left lung showed a markedly thickened pleura. The parenchyma was completely collapsed and showed many silicotic nodules with carbon in the centre and whirls of fibrous tissue at the periphery. The blood vessels and bronchioles were collapsed. The entire pulmonary parenchyma was apparently replaced by fibrous nodules and carbon, leaving nothing of the pulmonary structure but the larger bronchioles and blood vessels. Examination of many sections from different portions of the left lung failed to show any miliary tubercles (figure 3E).

The kidneys, spleen, liver and peritoneum were densely infiltrated with miliary tubercles. The prostate was caseous throughout. Many tubercles were seen at the base of the brain and along the Sylvian fissures.

*Comment:* Case 2 was a haematogenous pulmonary tuberculosis and case 3 was a generalized miliary tuberculosis. Though the tubercle bacilli were apparently carried from the general venous circulation to either lung in both cases, they found no suitable environment to become implanted in the completely collapsed lung (right upper and middle lobes in case 2 and left lung in case 3); favorable environment was limited in the partly collapsed lung (right lower lobe in case 2), and the environment was most suitable in the uncollapsed lung (left lung in case 2 and right lung in case 3). The anatomical and physiological factors involved were marked interference with the circulation and oxygen supply in the completely collapsed lung, some interference in the partly collapsed lung, and relatively no interference in the untreated lung.

## SUMMARY

Three cases of pulmonary tuberculosis treated with pneumothorax were presented. One case was complicated by bronchogenic dissemination, one by haematogenous pulmonary spread, and one by miliary generalized tuberculosis. All three cases came to postmortem examina-

tion soon after the complication developed. An attempt was made to interpret the mode of involvement in relation to the extent of collapse of the lung.

## CONCLUSIONS

Though the number of cases studied is small the following conclusion is suggested: the extent of involvement of a collapsed lung in the course of a haematogenous or bronchogenic dissemination is in inverse proportion to the degree of collapse present at the time of the dissemination.

## REFERENCES

(1) FORLANINI: In tema di pneumotorace artificiale pleuropneumonolisi totale, Riv. d. publicazioni pneumotorace therap., 1909, no. 6.
(2) LINDBLOM, S. G.: Zur Kenntnis der Heilung der Lungentuberkulose bei Pneumothoraxbehandlung, Beitr. Klin. Tuberk., 1922, *52*, 1.
(3) PINNER, M.: Personal communication.
(4) ASCHOFF, L.: Vorträge über Pathologie, Verlag von Gustav Fischer, Jena, 1925, p. 345.

# TUBERCULOUS BACILLAEMIA IN RABBITS[1]

## 1. Bacillaemia in Nonallergic Animals

JACQUES P. DUCHAINE[2]

When a small amount of tubercle bacilli is injected under the skin of an experimental animal the microörganisms very quickly reach the draining lymph nodes; here they multiply and after a certain interval, depending on the amount and virulence of the infecting microörganisms, are disseminated by means of the lymph and blood to the various tissues, where they will produce secondary foci.

Different investigators have tried to determine the time of appearance of these bacilli in the blood-stream and the importance of secondary focalization, either by culturing a certain amount of blood recovered at various intervals of time or by injecting the blood into guinea pigs. Lately, most workers have used the Loewenstein method of blood culture, which consists of inoculation of the Loewenstein medium following treatment of the blood with a weak acid (3 to 5 per cent acetic or 15 per cent sulphuric acid) and repeated washing of the sediment with distilled water in order to remove the haemoglobin, which, according to Loewenstein, inhibits the growth of tubercle bacilli.

When the results of experimental studies of this type are analyzed, a great deal of controversy is apparent. Some investigators record uniformly negative results. On the other hand, Anderson (1), in 1909, demonstrated tubercle bacilli in the heart blood of 7 out of 8 rabbits, inoculated 14 to 27 days previously with a pure culture of bovine bacilli, the exact amount not being mentioned. Mishulow and Park (2) inoculated a rabbit intravenously with 50 mgm. of a human strain and cultured whole blood withdrawn at various intervals from the ear on Loewenstein's medium and on the Bordet-Gengou medium. They found a very sharp decrease of bacillaemia, which occurred between 21 and 24 hours after inoculation; nevertheless a certain number of microörganisms could be found constantly in the blood, the amount rising sharply just before death.

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Graduate-Fellow of the C.R.B. Educational Foundation, Inc.

In another experiment the same authors (3) tested the blood from a rabbit injected intraperitoneally with 4 mgm. of a virulent bovine strain and found only one positive result; this occurred on the day of death, 115 days after infection.

Out of 34 samples of blood taken from the ear vein of 5 rabbits infected with a bovine strain, Manteufel and Kottmann (4) demonstrated macroscopical growth in only four instances; in these cases growth was obtained within the last four weeks of life of the animals.

Shapiro (5) inoculated 4 rabbits intravenously with 8 mgm. of a bovine strain; at various intervals the heart blood was cultured by the Loewenstein technique. Results varied, but were positive the first two days in 2 animals and negative on the 7th, 8th and 10th day respectively in 3 animals. In another series of rabbits inoculated with 17 mgm. of bovine type tubercle bacilli, bacillaemia was readily demonstrated by the Loewenstein method in all samples but one.

Corper and Vidal (6) injected various amounts of human, bovine and avian strains intravenously in guinea pigs, rabbits, chickens and dogs. They concluded that, whereas large amounts produce a constant bacillaemia, with small quantities (from 0.001 to 0.000,001 mgm.) the bacilli disappear rapidly from the circulation. In rabbits inoculated with a bovine strain their results were constantly negative, except with a dose of 1 mgm. and this only for two days after the injection.

Choun (7), testing the new Kirchner method of blood culture, recorded 30.1 per cent of positive results in rabbits infected with a virulent bovine strain, the amount injected being 0.01 mgm. intravenously and 10 mgm. subcutaneously. The animals were bled at regular intervals either from the ear vein or from the heart.

Guischard (8) infected rabbits intravenously with a virulent bovine strain, the amount of which was not reported. He was able to detect bacilli in the blood-stream only during the first 9 to 11 days after infection. It is noteworthy that each time the cultures or the guinea-pig inoculations were positive, acid-fast bacilli could be detected in the direct smears of the material used.

Strempel (9) injected rabbits intravenously with human and bovine strains in amounts varying from 1 to 10 mgm. He was able to recover bacilli from the heart blood only during the first two weeks. After that period, the cultures were always negative. A large dose of bovine bacilli (10 mgm.) injected subcutaneously failed to produce bacillaemia except soon after the injection and on the days preceding death.

In 3 rabbits inoculated intramuscularly with 1 mgm. of a bovine strain, Herta Schwabacher (10) demonstrated bacillaemia only on one occasion (after 5 days), after repeated examinations of venous blood from the ear at intervals of 5 to 83 days. In 3 rabbits inoculated intravenously with 5 mgm.

of a bovine strain, bacillaemia was demonstrated on all occasions; on the other hand, one animal inoculated intravenously with a much smaller amount of bacilli (0.01 mgm.) never showed any evidence of infection in the blood.

It is very difficult to correlate the results obtained by different workers. Some of them do not mention the amount of bacilli injected; others used such large doses of virulent microörganisms that the results obtained are obviously far removed from natural conditions.

Nevertheless there seems to be agreement on the following points: after an intravenous injection, there is a rapid clearing within a few hours of all microörganisms from the blood; thereafter, bacillaemia cannot be constantly demonstrated until shortly before death.

Only a few experiments have been published in which bacillaemia was investigated in animals injected with small doses of bacilli by the intramuscular or subcutaneous route. Most of the results obtained by different techniques were negative.

For these and similar reasons, it seemed worth while to take up again the whole problem of bacillaemia. A new method of testing the amount of bacilli in the blood-stream at a given moment was tried, the results being compared with those obtained by the Loewenstein technique.

Specific problems in this experiment were the following:

*1:* What is the course of bacillaemia in rabbits infected with a virulent bovine strain and inoculated (*a*) intravenously with a large dose of bacilli, (*b*) intravenously with a small amount of the same strain, and (*c*) subcutaneously with a medium-sized dose?

*2:* How reliable is the method used for detecting very small amounts of bacilli in the blood-stream?

The method chosen made use of a nonspecific local inflammation as a site for the detection of bacilli escaping from the blood-stream. The introduction of a sterile irritant into the pleural cavity produces an intense inflammation, dilating the capillaries and slowing the circulation, causing exudation of serum and cells. It was thought that an artificial exudation produced in the pleural cavity would filter out particles and foreign bodies circulating in the blood. Since it has been shown by Menkin (11) that with strong irritants the flow of lymph from the resulting inflammatory area is impeded, and that particles that have reached the inflammatory focus are trapped *in sutu* and fail to return to the circulation, a certain concentration of tubercle bacilli circulating in the blood can be expected at the site of such an inflammatory zone.

Indeed Kettle (12) has shown that tubercle bacilli circulating in the blood are localized at the site of inflammation. Similar observations were made by Ascoli (13). Thus it was thought that the introduction of an irritant in the pleural cavity would not only create a filter for the bacilli in the blood-stream, but that the induced inflammation would prevent them from returning to the general circulation.

Many attempts were made to determine the best irritant available and the most favorable time for tapping. Tests were made with:

(*1*) ***Saline solution:*** This provided little exudation and was too quickly resorbed.

(*2*) ***Aleuronat-starch suspension:*** (5 cc. of a suspension containing 5 per cent of aleuronat and 3 per cent of starch). This produced fluid containing many cells, and caused a strong fibrinous reaction of the pleura. Numerous masses of aleuronat imbedded in the fibrin can be mistaken at autopsy for caseous tubercles and render difficult close examination of the macroscopical appearance of the lungs.

(*3*) ***Terpinol:*** The injection of 2 cc., as advocated by Wagoner and Custer (14), caused a great amount of fluid but too strong a reaction in the parenchyma of the lungs, even, as in some cases, on the opposite side. The question then arose whether such a strong reaction would not be in itself a factor sufficient to mobilize bacilli from the tuberculous foci. Sections made at different levels in the lungs seemed to bear out this assumption. Therefore the results were discarded, and the animals treated by this method are not mentioned in this paper.

However, when the injection of terpinol was reduced to 0.2 cc., very good results were secured. By this method a large amount of clear, serous fluid can be recovered after 24 hours; the reaction of the pleura is mild and the lung tissue is not traumatized, as revealed by microscopical sections. These clearly show that the inflammation produced in the pleural cavity does not spread to the parenchyma of the lungs. As a matter of control, in a few cases sections made from both lungs were compared. There proved to be no reason for the belief that the irritant was in itself sufficient to cause waves of bacillaemia; this had not been the case when more than a slight amount of terpinol had been used.

The injection of the irritant into the pleural cavity must be made very accurately to prevent wounding the visceral pleura. A small slit was cut in the skin down to the subcutaneous tissue. The pleural space was found by pushing a very blunt needle adapted to a manometer. When the manometer showed definite negative pressure, about 30 to

40 cc. of air was injected into the pleural cavity in order to obtain a pressure of approximately zero. The irritant was not injected until the point of the needle was definitely felt to be loose in the cavity. Faulty injections (entrance of the irritant into the lung tissue) can be easily detected at autopsy, for the lung shows an area of pneumonia around the point of injection.

Difficulties in locating the pleural space may arise when the left cavity is injected in an animal previously injected in the right. This is not due to adhesions but to compensatory emphysema pressing the normal lung strongly against the ribs. Adhesions have never been encountered on the uninjected side, even in very sick animals.

Different methods of tapping were tried, namely, recovering 5 cc. of fluid every day for two to four days consecutively or recovering the whole amount of fluid 24 hours after the injection of the irritant. The latter method proved superior, but throughout the experiment the two techniques were used.

## EXPERIMENTAL PROCEDURES

Rabbits of approximately equal weight were infected with a given amount of 3 to 4 weeks old cultures on glycerin-agar of the virulent bovine strain Ravenel. At various intervals, 0.2 cc. of terpinol was injected into the pleural cavity by the method described above, and the fluid produced was recovered 24 hours later in 2 to 4 cc. of a 5 per cent solution of sodium citrate. The tubes were centrifuged for about 20 minutes at 3000 R/M, and the sediment was seeded without preliminary treatment on a series of tubes of Loewenstein's malachite-green medium containing bone marrow infusion (15), and incubated at 37°C. for at least eight weeks. The colonies growing at that time were counted and their number correlated with the amount of fluid cultured. The figures mentioned hereafter in this paper refer to the number of colonies present in 5 cc. of fluid.

At each tapping of the pleural fluid, as a control of the method used, 4 cc. of blood were drawn from the heart in 1 cc. of citrate solution and cultured by various methods: (*1*) by seeding the whole blood on the medium; (*2*) after treatment with repeated washings with distilled water; (*3*) after treatment with 5 per cent acetic acid. Special precautions were taken to avoid contamination by bacilli from the lung tissue during the process of withdrawing blood from the heart, since this organ is very much displaced in the thorax by the presence of fluid in the

pleural cavity. Two cc. of blood were drawn into a syringe and discarded. With the needle still in place but with a new syringe an additional 4 cc. of blood were withdrawn and used for culture after treatment.

In some cases, after a few weeks had elapsed, and when there was evidence that the compressed lung had resumed its normal functions, the same procedure was applied to the opposite side.

The animals were killed immediately after the last tapping and were closely searched for any evidence of faulty technique in the injection of the irritant or for signs of local infection at the site of the cardiac puncture; doubtful results were discarded.

TABLE 1

*Tubercle bacilli in artificial pleural exudate following intravenous injection of large amounts of virulent tubercle bacilli*

| ANIMAL NUMBER | AMOUNT OF TUBERCLE BACILLI INJECTED | TIME AFTER INFECTION WHEN BLOOD AND FLUID CULTURES WERE MADE | AVERAGE NUMBER OF COLONIES CULTURED FROM 5 CC. OF PLEURAL FLUID | AVERAGE NUMBER OF COLONIES CULTURED FROM 5 CC. OF BLOOD | AUTOPSY FINDINGS* |
|---|---|---|---|---|---|
| R 16 | 10 mgm. | 3½ hours | ** | 140 | No tuberculosis |
| R 17 | 10 mgm. | 5 days | ** | 5 | No tuberculosis |
| R 20 | 5 mgm. | 9 days | 338 | 1.25 | Numerous tubercles in spleen and lungs |
| | | 25 days | 70 | 5 | |
| R 19 | 10 mgm. | 13 days | 21,160 | contaminated | Generalized tuberculosis |

* The autopsies were performed on the same date on which blood and fluid were taken for cultures.

** Colonies were too numerous to be counted.

*Intravenous injection of bacilli:* Table 1 shows that a constant bacillaemia occurs in rabbits infected with a large amount of bovine type tubercle bacilli. Immediately after the inoculation, the number of bacilli in the blood-stream is very high, but it tends to diminish rapidly in the succeeding days, followed again by a rise as the infection proceeds.

Table 2, showing the effect of intravenous injection of small amounts of virulent bacilli, presents practically the same picture as the curve of bacillaemia in animals infected with a large dose. There is constant presence of bacilli in the blood-stream, as the results from the pleural fluid clearly show. It seems probable that these results reflect what happens in the general circulation; the frequently negative blood cultures may be attributed to the inadequacy of the technique and not to the

absence of blood infection. The reasons for this assumption will be discussed later.

As shown in table 2, after a very rapid clearing which has already been efficient in 24 hours, a few bacilli are constantly carried in the blood. In one case (rabbit RS 30) is seen the sharp rise prior to death which is always found in experiments carried until the animals die of tuberculosis. The other animals do not show the same rise of the curve, because they were sacrificed before the infection had killed them. At the given dosage, the Ravenel strain kills a rabbit in from eight to ten

TABLE 2

*Tubercle bacilli in artificial pleural exudate following intravenous injection of 0.01 mgm. of virulent tubercle bacilli*

| ANIMAL NUMBER | TIME AFTER INFECTION WHEN BLOOD AND FLUID CULTURES WERE MADE | AVERAGE NUMBER OF COLONIES CULTURED FROM 5 CC. OF PLEURAL FLUID | AVERAGE NUMBER OF COLONIES CULTURED FROM 5 CC. OF BLOOD | MACROSCOPICAL AUTOPSY FINDINGS* |
|---|---|---|---|---|
| | *days* | | | |
| RS 30 | 1 | 19 | 8 | Sacrificed dying; generalized tuberculosis |
| | 37 | 1,610 | ? | |
| RS 35 | 2 | 7 | 4 | No tuberculosis |
| RP 46 | 9 | 9 | 0 | Discrete generalized tuberculosis |
| | 20 | 3 | 0 | |
| RS 83 | 18 | 7 | 0 | A few tubercles in the lungs |
| RP 10 | 27 | 18 | 0 | Generalized tuberculosis |
| RP 11 | 34 | 23 | 0 | Generalized tuberculosis |
| RP 8 | 37 | 35 | ? | Generalized tuberculosis |

* The autopsies were performed on the same date on which blood and fluid were taken for cultures.

weeks. Differences in the individual resistance of the animals must naturally be taken into account.

*Subcutaneous injection of virulent bacilli:* A series of rabbits were injected subcutaneously in the right groin with 1.0 mgm. of the Ravenel strain. At various intervals a pleurisy was induced according to the technique previously described and the exudate was cultured. Blood cultures were made from the heart blood at the same time. Special emphasis has been accorded to the earliest appearance of bacilli in the blood-stream. As, in the first days after the infection, the cultures were repeatedly negative, controls were made by guinea-pig inoculations.

TABLE 3

*Tubercle bacilli in artificial pleural exudate following subcutaneous injection of 1 mgm. of virulent tubercle bacilli*

| INTERVALS OF TIME AFTER INOCULATION | RABBIT NUMBER | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 | 35 | 26 | 36 | 41 | 38 | 39 | 12 | 42 | 43 | 15 | 40 | 22 | 23 | 32 | 33 | 44 | 45 | 13 | 24 | 21 | 48 | 49 |
| 6 hours | 0 | | | | | | | | | | | | | | | | | | | | | | |
| 18 hours | | 0 | | | | | | | | | | | | | | | | | | | | | |
| 1 day | 0 | 0 | | | | | | | | | | | | | | | | | | | | | |
| 2 days | | | 0 | 0 | 0 * | | | | | | | | | | | | | | | | | | |
| 3 days | 0 | | 0 | 0 | 1 | | | | | | | | | | | | | | | | | | |
| 4 days | | | 0 | | | 0 | | | | | | | | | | | | | | | | 0 * | 0 * |
| 5 days | | | | | 0 | 0 | 0 | 0 | 0 | | | | | | | | | | | | | | |
| 6 days | | | | | 0 | 0 | 0 | | | 0 | 2 | 0 | | | | | | | | | | | |
| 7 days | | | 0 | | | 5 | 0 | | | | 4 | 0 | 0 | | 0 | | | | | | | | |
| 8 days | | | | | | | | | | | 2.5 | | | 0 | 0 | 0 | 0 | | | | | | |
| 9 days | | | | | | | | | | | | | 0 | | 1.8 | 1.25 | 0.35 | | | | | | |
| 10 days | | | | | | 1.5 | 0 | | | | | | | 0 | | | | | | | | | |
| 11 days | | | | | | | | | | | | | | | | | | 0 | | | | | |
| 15 days | | | | | | | | | | | | | | 1.25 | | | | | | | | | |
| 16 days | | | | | | | | | | | 0 | | | | | | | | | 0 | | | |
| 18 days | | | | | | | | | | | | | 0 | | | | | | | 0 | | | |
| 20 days | | | | | | | | | | | | | 0 | | | | | | | | | | |
| 26 days | | | | | | | | | | | | | | | | | | | 0 | | | | |
| 28 days | 0 | | | | | | | | | | | | | | | | | | 0 | | | | |
| 29 days | 0 | | | | | | | | | | | | | | 0 | | | | 1.5 | | | | |
| 32 days | | | | | | | | | | | | | | | 0 | | | | | | | | |
| 35 days | | | | | | | | | | | | | | 34 | | | | | | | | | |
| 36 days | | | | | | | | | | | | | | 50 | | | | | | 21 | | | |
| 37 days | | | | | | | | | | | | | | | | | | | | | | | |
| 39 days | | | | | | | | | | | | 4.35 | | | | | | | | 43 | | | |
| 42 days | | | | | | | 30 | | | | | | | | | | | | | | 41 | | |
| 44 days | | | | | | | | | | | | | | | | | | | | | 6.25 | | |
| 47 days | | 2 | | | | | | | | | | | | | | 0 | | | | | | | |

* Guinea pig inoculation negative.

Numbers refer to the number of colonies found in 5 cc. of pleural exudate.

Blood cultures, having been constantly negative, are not recorded here.

In these cases the specimens of fluid and blood were divided into equal parts, one-half being used for culture, the other half being injected into one or two guinea pigs.

Table 3 records the results of this experiment. As the cultures from the blood, and guinea-pig inoculation also, have been in every case negative, only the results obtained from the pleural exudate are mentioned.

The data in table 3 present a somewhat different picture from that seen in tables 1 and 2. Bacilli can be detected in the pleural fluid three days after the infection, at the earliest. From that time on, the disease is seen to spread slowly, probably through small, discrete discharges of a few bacilli at a time. It is likely that now and then, either through septic embolism or by phagocytic activity, a few bacilli appear in the general circulation but are quickly engulfed by the tissues. As the infection spreads, the tuberculous foci from which these septic waves have arisen grow more and more numerous, with a consequent increase in the number and importance of the waves of bacillaemia. After 5 or 6 weeks, under the conditions of the experiment, there is a constant overflow of bacilli into the blood-stream.

The fact that bacillaemia consists of sudden and discontinued discharges of bacilli is clearly indicated by the fact that in some cases (rabbit no. 32) the results were at first positive and later became repeatedly negative. This also explains why different authors record negative results from direct cultures from the blood. The moment at which the blood is withdrawn must coincide with the appearance in the blood-stream of one of those discharges, and it is now evident that the clearing process is quick and efficient until the infection becomes overwhelming.

If these results have been easier to obtain in our experiments it is due to the fact that the whole blood is in a way filtered *in vivo* during many hours; even then the number of bacilli recovered is very small. It is understandable, therefore, that a small amount of blood, containing so few bacilli, will give negative results.

## DISCUSSION AND CRITICISM OF THE METHOD USED

Throughout this experiment the view has been held that the observations made on the pleural fluid were the exact representation of what happens in the blood-stream. The inference has been emphasized that the bacilli found in the exudate had been brought there by the blood

and retained by the exudate produced by the irritant. But there is one, and a very important objection that immediately arises: are we dealing with bacilli traveling free in the circulation or with bacilli released by the inflammation from tuberculous foci involving the pleura?

In order to answer this question, the following experiment was undertaken.

Simultaneous cultures were made of the exudate and of a section of lung tissue bordering the visceral pleura. Directly after the tapping, the animal was killed by the ordinary means of injecting air into the vein. The thoracic cavity was opened aseptically and 200 mgm. of lung tissue were excised from the lower lobe on the side from which the pleural exudate had been withdrawn. The tissue was ground up with sterile sand and suspended in 10 cc. of saline solution. Three tubes of Loewen-

TABLE 4

*Comparison of number of tubercle bacilli in lung and artificial pleural exudate following subcutaneous injection of 1 mgm. of tubercle bacilli*

| ANIMAL NUMBER | TIME AFTER INFECTION WHEN FLUID AND LUNG TISSUE CULTURES WERE MADE | AVERAGE NUMBER OF COLONIES CULTURED FROM 5 CC. OF FLUID | NUMBER OF COLONIES CULTURED FROM 200 GM. OF LUNG TISSUE |
|---|---|---|---|
| | *days* | | |
| R 43 | 7 | 0 | 1,200 |
| R 44 | 9 | 1 | 1,170 |
| R 45 | 12 | 0 | 3,100 |
| R 40 | 40 | 4.35 | * |
| R 39 | 41 | 9 | * |

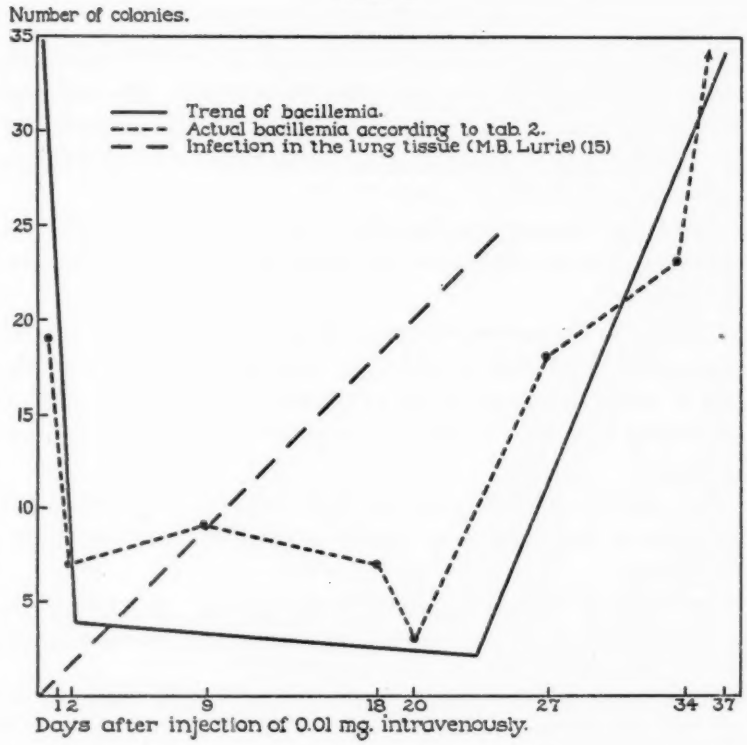
* Colonies were too numerous to be counted.

stein's medium were seeded with the sediment directly; another portion of the sediment was treated with 1 cc. of a 6 per cent sulphuric acid solution and incubated for about 20 minutes at 37°C., and three tubes of the same medium were planted after neutralization with potassium hydrate. The number of colonies growing were counted after 8 weeks in the incubator; when contamination of the untreated specimens prevented the recording of the results these were computed from the growth in the treated tubes, the calculation being made on the apparently justified assumption that the treatment allows only one-fifth of the growth obtained normally without treatment (16). The results are recorded in table 4.

It is clear that in the first twelve days following infection few if any tubercle bacilli can be found in the pleural fluid, although the lung

contains considerable numbers. Later, however, when the bacilli in the lungs have accumulated in tremendous numbers, and when the subpleural tubercles have undergone caseation with the development of a perifocal inflammation, significant numbers of tubercle bacilli can be found in the pleural fluid. Since a pleural exudate often contains some cells desquamated from the pleural lining it is plain that the

CHART 1.




interpretation as to the source of the bacilli in this pleural fluid remains subject to question.

However, if a composite chart is drawn (chart 1) showing the rate of accumulation of tubercle bacilli in the lung, as has been done by Lurie (17), and compared with the general trend of infection obtained from the pleural fluid after the same mode of inoculation, we see clearly that the two curves, far from showing any tendency to gross parallelism, cross one another in the first third of the graph. Therefore it cannot be said

with certainty that the bacilli cultured from the pleural exudate are all derived from the blood. On the other hand the extensive and generally accepted studies of Ranke, Hübschmann, Pagel and many others, which indicate that at intermittent intervals tubercle bacilli are shed into the blood-stream from advancing tuberculous lesions, support the view that most of the bacilli cultured from the pleural exudate were actually derived from the blood.

## SUMMARY AND CONCLUSIONS

1. A new method of detecting bacillaemia in rabbits infected with a virulent strain of tubercle bacilli has been tried. The value of this method is discussed. The method is based on the assumption that bacilli will tend to pass from the blood to the site of an artificial localized inflammation in the pleural cavity.

2. There is a constant bacillaemia in animals infected by the intravenous route, as indicated by the bacilli found in an artificially produced pleural exudate.

3. There is a discontinuous bacillaemia in animals infected by the subcutaneous route as indicated by the same method. This bacillaemia consists of small discharges of short duration carrying very few bacilli and appearing from time to time at irregular intervals during the course of the disease.

4. The number of bacilli cultured from the pleural exudate indicates a sharp rise of the number of bacilli in the blood-stream a few days prior to death.

5. That some of the bacilli present in the pleural exudate may be shed directly from the subpleural pulmonary lesions has not been excluded.

The author wishes to acknowledge his indebtedness to Dr. M. B. Lurie and Dr. E. R. Long for their valuable advice and to Miss Nelle Morley and Miss Mabel Seibert for their technical assistance.

## BIBLIOGRAPHY

(1) ANDERSON: Hyg. Lab. Bull., Washington, 1909, no. 57, p. 7.
(2) MISHULOW, L., AND PARK, W. H.: Jour. Prev. Med., 1932, *6*, 95.
(3) MISHULOW, L., AND PARK, W. H.: Bacillaemia in rabbits following subcutaneous and intraperitoneal inoculation, Amer. Rev. Tuberc., 1933, *28*, 875.
(4) MANTEUFEL AND KOTTMANN: Ztschr. Immunitätsforsch., 1932, *74*, 25.
(5) SHAPIRO: Ztschr. Tuberk., 1932, *66*, 248.
(6) CORPER, H. J., AND VIDAL, C. B.: Tuberculous bacillaemia. Experimental studies with three pathogenic types of tubercle bacilli, Amer. Rev. Tuberc., 1935, *32*, 575.

(7) CHOUN, C. K.: Cultural demonstration for study of bacillemia in experimental tuberculosis, Beitr. z. Klin. Tuberk., 1933, *83*, 190.
(8) GUISCHARD: Ibid., 1932, *80*, 285.
(9) STREMPEL, W.: Bacillemia in experimental animals, Zentralbl. f. Bakt. (Abt. 1), 1935, *133*, 159.
(10) SCHWABACHER, H.: In Tuberculous bacillaemia by WILSON, G. S., Privy Council: Medical Research Council, London, 1933.
(11) MENKIN, V.: Studies on inflammation, Jour. Exper. Med., 1929, *50*, 171; 1930, *51*, 285; 1930, *51*, 879.
(12) KETTLE, E. H.: Brit. Jour. Exper. Path., 1924, *5*, 158.
(13) ASCOLI, A.: Ancora sul fenomeno della anacoresi: Biochemica e terapia sperimentale, 1931, fasc. ix, 18.
(14) WAGONER, G., AND CUSTER, R. P.: Handbook of experimental pathology, C. C. Thomas, Springfield, Ill., 1932.
(15) LURIE, M. B.: The fate of BCG and associated changes in the organs of rabbits, Jour. Exper. Med., 1934, *59*, 163.
(16) DUCHAINE, J. P., AND LURIE, M. B.: The fate of tubercle bacilli in the organs of reinfected rabbits, Ibid., 1929, *50*, 747.
(17) LURIE, M. B.: The fate of human and bovine tubercle bacilli in various organs of the rabbit, Jour. Exper. Med., 1928, *48*, 155.

# TUBERCULOUS BACILLAEMIA IN RABBITS[1]

## 2. Bacillaemia in Allergic Animals

JACQUES P. DUCHAINE[2]

In a previous paper (1) the results of a series of experiments on tuberculous bacillaemia in rabbits were recorded. These were obtained by a new method, the value of which was discussed.

It is now my aim to record the influence of allergy on the bacillaemia occurring in rabbits infected with the same virulent strain of bovine tubercle bacilli as in the previous experiments.

In spite of the importance of this topic, very little work has hitherto been published; and all the workers have used guinea pigs, probably for the reason that bacillaemia is easier to detect in these animals than in rabbits.

Ninni and Sanctis Monaldi (2) injected guinea pigs intraperitoneally with 1 mgm. of tubercle bacilli after having vaccinated them with an injection of BCG. Culturing the blood at regular intervals, they were able to show a much reduced rate of bacillaemia in the animals treated with BCG compared with controls. Using smaller doses (0.01 mgm.), they were unable to detect bacilli in the blood of the treated animals after 24 hours, whereas the controls showed evidence of bacillaemia for at least 10 days. Bacanu and Pezzangora (3) and Boquet and Laporte (4), working along the same line, reached the same conclusions.

A brief summary of our previous conclusions is here indicated.

It was found (1) that the artificial induction of an aseptic exudation in the pleural cavity resulted in the retention at the site of inflammation of bacilli circulating in the general circulation. By tapping and culturing this exudate after a few hours, a fairly accurate picture could be obtained of the extent of bacillaemia at a particular moment. It was concluded that a slight but constant bacillaemia occurred in animals injected intravenously with amounts as small as 0.01 mgm. On the other hand,

[1] From the Laboratory of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois, and the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Graduate-Fellow of the C.R.B. Educational Foundation, Inc.

subcutaneous injections of even a larger dosage called forth only an inconstant flow of bacilli in the blood-stream, consisting in small discharges of microörganisms varying in amount and in frequency of discharge.

The aim of this paper is to evaluate the effect of the general changes due to allergy upon these bacillary discharges.

Reliance could be placed only on the intravenous route, as the experiment involves the use of control animals. As pointed out, animals injected by other routes show a few waves of bacillaemia, the inconstancy of which renders them unsuitable for control experimentation. As both series should be tried simultaneously, there would be very little probability of one of those discharges occurring in both series of animals at exactly the same time.

## METHOD

Allergy was induced by BCG vaccination. Two series of rabbits of approximately the same weight were used. One of them was given an intravenous injection of 5 mgm. of BCG. Nine weeks later, when, as Lurie (5) has shown, the avirulent bacilli had completely disappeared from the circulation, both series were injected intravenously with 0.01 mgm. of the virulent Ravenel strain, 3 to 4 weeks old and growing on Loewenstein's medium. In a few instances where there was a discrepancy of weight between the vaccinated animals and the controls, the amount of virulent tubercle bacilli injected was adjusted accordingly.

At regular intervals, 0.2 cc. of terpinol was injected in the pleural cavity of one vaccinated animal and of one control. After 24 hours, the pleural cavity was tapped dry and the exudate seeded after centrifugation, but without preliminary treatment, on Loewenstein's malachite-green medium and incubated for at least 8 weeks at 37°C.

At the end of this period, the number of colonies growing was counted and the results calculated for the amount of fluid recovered. In table 1 the number of colonies recorded is that in 5 cc. of pleural exudate.

## DISCUSSION

Without discussing the value of the method used in the course of this experiment (for possible objections see preceding paper) I shall only emphasize the results recorded in table 1.

It is known from previous experiments that a slight bacillaemia can always be detected in rabbits injected intravenously. After a very sharp decrease following the injection, only a small number of microörganisms

are consistently found in the blood. On this background of a discrete bacillaemia, we may sometimes witness the discharge of a much greater wave carrying bacilli in considerable numbers; this is probably due to the sudden breakdown of a tuberculous focus and subsequent embolism. This is illustrated in rabbit R 94. In this particular case no other reason has been found to account for the great number of bacilli found in the boood-stream, as compared with 16 days previously. The animal was sacrificed the same day as the second tapping was made. The lungs were carefully searched for any evidence of perforation of the visceral pleura which might account for the release of bacilli from the lung into the exudate; nothing was found that could corroborate this idea.

TABLE 1

| INTERVAL BETWEEN INFECTION AND CULTURE OF PLEURAL EXUDATE | NONALLERGIC ANIMALS | | ALLERGIC ANIMALS | |
|---|---|---|---|---|
| | Animal number | Average number of colonies cultured in 5 cc. of fluid | Animal number | Average number of colonies cultured in 5 cc. of fluid |
| *days* | | | | |
| 1 | RS 30 | 19 | R 91 | 1 |
| 2 | R 35 | 10 | R 37 | 5 |
| 3 | R 94 | 10 | R 87 | 1.75 |
| 4 | R 95 | 2.50 | R 88 | 0.35 |
| 8 | R 97 | 17 | R 89 | 0 |
| 9 | RP 46 | 17 | RP 30 | 0.8 |
| 15 | R 99 | 3.31 | R 90 | 2 |
| 18 | R 83 | 0.7 | R 92 | 0.45 |
| 19 | R 94 | 127 | R 87 | 1 |
| 20 | RP 46 | 3 | RP 30 | 0 |
| 29 | R 97 | 6.5 | R 89 | 1 |
| 36 | R 98 | 9 | R 88 | 42 |
| 41 | R 35 | 31 | RP 31 | 12.5 |

In the case of animal R 88, the explanation is clearer. The rabbit was very sick at the time of the second tapping and advanced tuberculous lesions were found in every organ at autopsy.

When the trend of bacillaemia in the nonallergic and in the allergic animals is compared, a great reduction in the number of bacilli recovered from the immunized animals is apparent. Except in one case which has been accounted for (R 88), the numbers in the allergic animals are very much smaller than in the controls. Whereas, during the first nine days, the bacillaemia in the controls remains practically at the same level, in the allergic animals the clearing process has been efficient in removing bacilli from the general circulation.

In a later phase, when in nonvaccinated animals the disease is progressing in the tissues, again we see that the allergic animals are much more efficient in preventing contamination of the blood-stream. It is thus apparent that one of the effects of allergy is to enable the tissue reaction to free the general circulation more rapidly of the invading microörganisms. Following this, there occurs an enhanced capacity of the tissues to anchor and retain them and to prevent them from disseminating. It would appear that it is only when the general breaking down of the tissue immunity occurs, under the stress of the growing infection, that the blood is invaded by large numbers of bacilli in both series of animals.

Ever since the fundamental researches of Krause and Willis, many workers, including Opie, Rich, Lurie, Menkin, Calmette, Boquet and others, have made it clear that allergy plays an important rôle in localizing the lesions in experimental infections where the amount of bacilli injected is very great. The view seems justified, therefore, that the process is still more efficient in conditions encountered in human disease, where slight infections are the rule.

## SUMMARY AND CONCLUSIONS

1. A test of tuberculous bacillaemia has been made in allergic and nonallergic rabbits by producing a pleural exudate and culturing it at regular intervals for tubercle bacilli. The allergy was induced by BCG vaccination.

2. Under the conditions of experimentation, a constant bacillaemia has been found in the nonallergic animals. In the allergic animals, an inconstant bacillaemia can be detected. In twelve out of thirteen rabbits the number of bacilli recovered was much less in the allergic rabbits than in the controls.

3. Tubercle bacilli injected in the general circulation tend to disappear from the blood much more rapidly in allergic than nonallergic animals. This clearing process requires about ten days in the latter, whereas in the former group, it is efficient within 24 hours.

4. Allergic animals show an enhanced ability to anchor and retain bacilli finding their way into the general circulation during the course of the disease. Allergy thus reduces the dangers of dissemination through the blood.

I am indebted to Dr. Henry C. Sweany for valuable advice given in the performance of this work.

## BIBLIOGRAPHY

(1) DUCHAINE, J. P.: Tuberculous bacillaemia in rabbits. 1. Bacillaemia in nonallergic animals, Amer. Rev. Tuberc., 1938, *37*, 507.

(2) NINNI, C., AND DE SANCTIS MONALDI, T.: Curve of bacillemia in guinea pigs vaccinated with BCG vaccine and tested by the peritoneal route, Compt. rend. Soc. de biol., 1933, *113*, 377.

(3) BACANU, C., AND PEZZANGORA, F.: La dispersion du bacille de Koch dans la primo-et surinfection des cobayes inoculés par voie intraganglionaire, Ibid., 1935, *120*, 1061.

(4) BOQUET, A., AND LAPORTE, R.: Sur la dispersion des bacilles de surinfection dans l'organisme des cobayes tuberculeux, Ibid., 1936, *121*, 211.

(5) LURIE, M. B.: The fate of BCG and associated changes in the organs of rabbits, Jour. Exper. Med., 1934, *60*, 163.

# THE FLOTATION METHOD OF SPUTUM EXAMINATION[1]

C. RICHARD SMITH

That liquid hydrocarbons may be used to separate tubercle bacilli from a watery suspension was first observed by Lange and Nitsche (1) in 1909 and applied by them to sputum examination. They liquefied the sputum with alkali, added water, and then shook it vigorously with ligroin. After standing, the ligroin separated out at the top and the tubercle bacilli were found in the "border scum" just beneath the hydrocarbon layer. By this hydrocarbon-extraction-flotation process they were able to demonstrate acid-fast bacilli in several sputa negative by direct smear.

The principle of Lange and Nitsche has since been applied to sputum examination with various modifications. Bernhardt (2) substituted antiformin for alkali as a sputum solvent. Loeffler (3) used antiformin and chloroform, separation of the chloroform into a subnatant layer being hastened by centrifuging. Kinyoun (4) used an alkaline solution of hypochlorites and ligroin, shaking by machine and centrifuging. His procedure showed an increased efficiency of 19 per cent over direct smear examination.

Sodium hydroxide, gasoline or xylol, extensive dilution, mechanical shaking, gravity separation and picric acid as a counterstain are the essentials of Pottenger's method (5). Pottenger emphasizes the importance of distribution of the tubercle bacilli. Clumps of bacilli, he believes, are broken up by the solvent action of the hydrocarbon on interbacillary wax-like cement substances. He found 60 times as many tubercle bacilli in flotation as in direct smears and was able to detect as few as 1,000 organisms present in a 24-hour specimen.

The superiority of picric acid over blue and green counterstains was first noted by Spengler (6).

Andrus and MacMahon (7), using sodium hydroxide, chloroform and centrifugal separation, claimed bacillary increases of 90 to 240 times, as compared to increases of only 3 to 4 times obtained by them with the common sedimentation methods. Of 106 patients never positive by

[1] From the Barlow Sanatorium, Los Angeles, California.

smear, these authors found 58 per cent positive by chloroform extraction. The chloroform technique even proved superior to guinea-pig inoculation in their hands.

## PROCEDURE

The procedure used is essentially that of Pottenger (5). The sputum of three days is collected in an 8-ounce, wide-mouth bottle and shaken five minutes by machine, with an equal amount of 0.5 per cent sodium hydroxide. After incubation in a water bath for 30 minutes at 55°C., any debris collected at the bottom is pipetted off. The specimen is diluted to about 200 cc. with distilled water and shaken five minutes with 0.5 to 1 cc. of xylol. On standing a half hour or more, a cream-like layer forms at the top. This "cream" is skimmed off with a pipette equipped with a rubber bulb and the pipette placed in a rack at an angle of 45° for further layering. The clear subnatant-liquid is returned to the bottle and the drop of cream spotted on a glass slide which is kept on a covered water bath at 60°C. The skimming process is repeated until a spot three to six layers deep and about 1 cm. in diameter is obtained, each drop being allowed to dry before the next is added. The smear is washed with ether, stained ten minutes with carbol-fuchsin on the water bath, decolorized one to two minutes with 3 per cent hydrochloric acid in alcohol and counterstained with 1 per cent aqueous picric acid.

## EXPERIMENTAL

1. To gain some idea of the increase in the number of tubercle bacilli shown by the flotation test, as compared with the direct smear, from a selected sputum particle, seven consecutive preparations in which the direct smear showed one or more bacilli were chosen. Direct and flotation smears were each examined ten minutes.

Table 1 shows tremendous variation in the comparative counts from an actual superiority for the direct smear to an advantage of 1,100 times for the flotation smear. The average increase of flotation over direct smear is 85 times.

2. To get some idea of the minimum quantity of tubercle bacilli detectable by the flotation test, we prepared sputa containing known amounts of bacilli. The tubercle bacilli were obtained from two to six weeks old cultures grown on a solid medium. They were weighed out, ground into suspensions, and mixed with 10 cc. portions of known nega-

tive sputum by shaking. Results of routine flotation tests are shown in table 2.

Tubercle bacilli in a concentration of .000,001 mgm. per cc. of sputum were demonstrable by the flotation test in two out of three trials. In one out of two trials at a concentration of .000,000,1 mgm. per cc., one bacillus was found.

TABLE 1

| SPUTUM SPECIMEN | NUMBER OF BACILLI FOUND IN TEN MINUTES | |
|---|---|---|
| | Direct smear | Flotation smear |
| 1 | 3 | 130 |
| 2 | 1 | 1,100 |
| 3 | 4 | 3 |
| 4 | 1 | 40 |
| 5 | 5 | 4 |
| 6 | 1 | 100 |
| 7 | 1 | 13 |
| Average per slide..... | 2.3 | 197 |

TABLE 2

| MGM. OF BACILLI PER CC. OF SPUTUM | TRIAL 1 | TRIAL 2 | TRIAL 3 |
|---|---|---|---|
| | Strain 24, four weeks old | Strain 65, two and one-half weeks old | Strain 81, six weeks old |
| .01 | | 33 per min. | |
| .000,1 | | 14 in 5 min. | 90 in 5 min. |
| .000,01 | 5 in 10 min. | | 19 in 5 min. |
| .000,001 | 2 in 10 min. | 0 in 15 min. | 3 in 20 min. |
| .000,000,1 | 0 in 10 min. | | 1 in 13 min. |
| .000,000,01 | | 0 in 10 min. | |
| .000,000,001 | | | 0 in 7 min. |
| Control | | 0 in 10 min. | 0 in 14 min. |

3. To determine the importance of saprophytic acid-fast microörganisms as a source of error in sputum examination, the sputum of healthy employees, known not to have tuberculosis, was placed in a closed bottle and kept on a laboratory shelf. Flotation and cultural examination was made at intervals. At twenty-three days and thereafter up to four and one-half months a variety of acid-fast microörganisms were demonstrable by flotation and culture. In the flotation smears they appeared as cocci, diplococci, bizarre rod forms, as well as forms indistinguishable from tubercle bacilli.

Culture in no case showed typical colonies of tubercle bacilli. Three atypical growths were recovered: (*a*) smooth, glossy, smeary, yellow colonies showing, microscopically, acid-fast diplococci and irregularly shaped acid-fast rods with rounded ends, some of which were beaded; (*b*) smooth, dull, smeary, cream-colored colonies showing tiny, rather thick acid-fast rods; (*c*) smooth, glossy, smeary, bright orange colonies containing pale acid-fast rods of variable thickness, with or without deep-staining beads. Growths *a* and *b* were lost; *c* was inoculated into a guinea pig without the development of tuberculosis.

## RESULTS IN THE ROUTINE USE OF THE FLOTATION TEST

Within two years, 1,248 sputum specimens from 260 persons have been examined simultaneously by direct smear and xylol flotation.

TABLE 3

*Direct smears examined three minutes, flotation smears ten minutes*

| | TESTS | PERSONS |
|---|---|---|
| Total | 1,248 | 260 |
| No tuberculosis | 124 | 30 |
| Apparently cured | 30 | 27 |
| Arrested | 52 | 39 |
| Negative by direct smear | 1,170 | 218 |
| Negative direct smear, positive flotation | 272 (23%) | 64 (29%) |
| Positive direct smear, positive flotation | 77 | 54 |
| Positive direct smear, negative flotation | 1 | 0* |
| False positives | 0 | 0 |

* Subsequent flotation tests were positive in this patient.

Eleven hundred and twenty-six of the specimens were from 158 resident sanatorium patients, 126 from 93 expatients and 12 from 9 other persons suspected of having tuberculosis. Usually the sputum of inpatients was examined by flotation only where the direct smear had been negative for one or more months.

Direct smears from likely particles or from the sputum-sodium-hydroxide mixture were made on the same slide as the flotation smear and stained in the same way. Direct smears were examined a minimum of three minutes, flotation smears a minimum of ten minutes or until found positive. In patients never positive before, the finding of at least 7 typical acid-fast bacilli in one specimen, or less than this in three specimens, was required for a positive report.

To get a fairer evaluation, a series was run in which both direct and flotation smears were examined three minutes and all direct smears were made from likely particles. Three hundred and eighty-eight simultaneous tests were made on the sputa of 159 persons. For the purposes of this comparison all smears showing one or more bacilli are called positive. Results are shown in table 4.

In the second series, excluding the results for nontuberculous, apparently cured and arrested cases, the flotation test showed 19 per cent more sputa and 28 per cent more persons positive than the direct smear.

Among 158 sanatorium patients included in this study, 23 never positive by repeated direct smears were positive one or more times by flotation. Thirty-one patients were positive for the first time by the flotation test.

TABLE 4

*Direct and flotation smears, each examined three minutes*

| | TESTS | PERSONS |
|---|---|---|
| Total | 388 | 159 |
| No tuberculosis | 60 | 17 |
| Apparently cured | 8 | 8 |
| Arrested | 19 | 16 |
| Negative by direct smear | 364 | 137 |
| Negative direct smear, positive flotation | 53 (14%) | 27 (19%) |
| Positive direct smear, positive flotation | 23 | 22 |
| Positive direct smear, negative flotation | 0 | 0 |
| False positive | 0 | 0 |

Four patients were admitted to the Sanatorium in whom the presence of active intrapulmonary disease was highly questionable. Direct smears were negative. Flotation tests proved them to have tuberculosis.

In another group of 6 patients, resident for several months or years, physical signs and X-ray pictures showed evidence of healing. Sputum examination by direct smear was negative. Were these patients ready to go home or to go to work? The flotation test revealed all to have positive sputum.

In patients subjected to some form of surgical collapse of the lung, X-ray pictures and other clinical procedures cannot be depended upon to disclose the state of the disease. Here we have found the flotation test of great value. We have had 13 cases of pneumothorax, one case of oleothorax, and 3 cases of thoracoplasty in which X-ray pictures

indicated complete collapse of the lesions and in which the sputum was negative by direct smear but positive by flotation.

Among 173 patients subjected to some form of collapse therapy, sputum smears were negative and flotation tests positive at six months in 16; six to twelve months in 18; one to two years in 16; and two to three years in 8.

## DISCUSSION

We have made no direct comparison between the flotation test and other concentration methods. The significant features of the test are improved distribution of tubercle bacilli and cleaner smears.

Distribution is a little recognized factor. Often it is more important than concentration. All the tubercle bacilli in a given sample may be contained in one small particle of sputum. To find these microörganisms more surely, distribution rather than concentration is desired. Not infrequently, more acid-fast bacilli are demonstrable by the direct than by the flotation smear, as shown in table 1. On the other hand, the flotation test is almost always positive when the direct smear is positive. Among 1,248 simultaneous tests, direct smear was positive and flotation negative in only one instance (table 3). The *number* of bacilli found in the concentration smear is not nearly as important as the certainty of finding *some* bacilli.

Concentration tests, using the principle of sedimentation, have the disadvantage of concentrating other particulate matter as well as tubercle bacilli. Dirty smears are the result. The debris hides tubercle bacilli and makes examination more difficult. Flotation smears are relatively clean.

Whether flotation or sedimentation produces the greatest concentration of tubercle bacilli, I don't know. Hydrocarbon flotation is capable of remarkable concentrating powers as shown by the ability to demonstrate as little as .000,001 mgm. of tubercle bacilli per cc. in a sputum sample of average size.

The comparisons made between routine direct and flotation smears do not show the advantages attributable to picric acid as a counterstain, since both were stained in the same manner. Green and blue counterstains give a better contrast and, of course, show secondary microorganisms and cells present. On the other hand, they render opaque overlying cells and debris which may obscure many tubercle bacilli. Picric acid, a diffuse, nonselective stain, leaves the smear clear and transparent, enabling one to examine all depths. All extraneous matter

is stained an even blank yellow and acid-fast microörganisms stand out prominently.

The possibility of error due to incorrect staining and cross-contamination is recognized. Insufficient decolorization is as dangerous as over decolorization. We have found that flotation smears will stand fifteen minutes of exposure to acid alcohol and that thirty minutes is required to cause a perceptible loss in the bacillary count. All glassware used is baked at a temperature high enough to destroy adherent tubercle bacilli. Only new corks are used.

We believe the occasional presence of acid-fast saprophytes in sputum to be a very real source of error in any concentration test. These microorganisms are ubiquitous. They have been found in grass, soil, air and water supplies. We have found them fairly often in routine sputum cultures and they are frequently seen in flotation smears. Ordinarily they are few in number but multiply rapidly during warm weather. Most of them are distinguishable morphologically. To avoid error, only typical, slender, acid-fast bacilli are counted. In questionable cases, laboratory consultations are held. Culture provides a good check. In 1,248 flotation tests, it is believed, there are no false positive reports.

The flotation test is little if any more complicated than other concentration methods. The sputum remains in the collection bottle throughout the procedure. Results are obtained the same day.

There are many reports in the literature showing the superiority of one or another concentration test over direct smear examination. In very few is the time of examination mentioned while, often, the two tests are not run on the same specimen. In the first series, shown in table 3, results are given as reported on the patients' charts. Comparison here is not fair because of the difference in time of examination. In the second series (table 4), however, a well controlled comparison is presented. The flotation test shows a superiority of 14 per cent for individual specimens and 19 per cent for persons examined; a corrected superiority of 19 and 28 per cent respectively. We submit these results as a reasonable estimation of the worth of the hydrocarbon flotation test in sputum examination.

## SUMMARY

1. The results of examination of 1,248 sputum samples from 260 persons, simultaneously, by direct smear and by the flotation test are reported.

2. Fourteen per cent of smear-negative specimens and 19 per cent of smear-negative persons were positive by flotation.

3. Flotation smears showed an average of 85 times as many acid-fast bacilli as direct smears.

4. Tubercle bacilli in concentrations as low as .000,001 mgm. per cc. in a 10 cc. specimen of sputum are demonstrable by the flotation test.

5. Nonpathogenic acid-fast microörganisms are frequently present in sputum and may be confused with tubercle bacilli.

6. The advantages of flotation over sedimentation procedures are better distribution of tubercle bacilli and cleaner smears.

7. The flotation test has proved of great value in the diagnosis and prognosis of those cases having very few tubercle bacilli in the sputum, particularly where collapse therapy has been used and X-ray pictures are not dependable.

## REFERENCES

(1) Lange, L., and Nitsche, P.: Eine neue Methode des Tuberkelbazillennachweises, Deutsch. med. Wchnschr., 1909, *35*, 435.

(2) Bernhardt, G.: Ueber die Verwendung von Antiformin und Ligroin für den Nachweis der Tuberkelbazillen im Sputum, Ibid., 1909, *35*, 1428.

(3) Loeffler, F.: Ein neues Anreicherungsverfahren zum färberischen Nachweise spärlicher Tuberkelbazillen, Ibid., 1910, *36*, 1987.

(4) Kinyoun, J. J.: A note on Uhlenhuth's method for sputum examination for tubercle bacilli, Amer. J. Pub. Health, 1915, *5*, 867.

(5) Pottenger, J. E.: The demonstration of rare tubercle bacilli in sputum, Amer. Rev. Tuberc., 1931, *24*, 583.

(6) Spengler, C.: Neue Färbemethoden für Perlsucht and Tuberkelbazillen und deren Differentialdiagnose, Deutsch. med. Wchnschr., 1907, *33*, 337.

(7) Andrus, P. M., and MacMahon, H. E.: The use of volatile hydrocarbons in the concentration of tubercle bacilli, Ibid., 1924, *9*, 99.

# THE CLINICAL VERSUS THE PUBLIC HEALTH POINT OF VIEW IN THE TREATMENT OF TUBERCULOSIS[1]

F. M. POTTENGER

## INTRODUCTION

Medicine has separated into two closely related groups of physicians—the practitioners of clinical medicine and the administrators of Public Health. The one, composed of private physicians, is particularly the guardian of the lives of the individuals who are ill; the other, composed of physicians occupying official positions responsible to government, is particularly the protector of the lives of the well. One holds the interest of the patient as paramount; the other, the interest of society.

Public Health, being the offspring of clinical medicine, is younger and therefore biologically the more aggressive. While Public Health, as we know it to-day, was born with bacteriology and so is only a little more than fifty years of age, clinical medicine is more than twenty centuries old. However, clinical medicine is not suffering from the inertia of age, for recently it has been reincarnated with a scientific basis. Its rebirth not only made medicine more efficient but also made possible the birth and present day conception of Public Health. For fifty years these great forces in civilization have been each increasing its own efficiency; and, together, they have marched forward battling for the health, happiness and success of the people.

Where two forces of such strength and individuality, of such importance to mankind, are occupying fields and pursuing purposes which of necessity overlap, it is inevitable that some conflict should arise, for each is jealous of its own prerogatives and seeks to protect its own province. So, without it being carefully analyzed and openly recognized, a conflict of opinion is arising between practitioners of medicine and the administrators of Public Health as to what should be the dividing line between their activities; or, rather, to what extent and in what particulars they should overlap.

The conflict is particularly in evidence where clinical medicine and

[1] Read at the joint meeting of the American Therapeutic Society and the Atlantic County Medical Society, Atlantic City, New Jersey, June 4, 1937.

Public Health come together in dealing with infectious diseases. It not only requires that the province of these two forces be more accurately established but also that the rights of individuals as compared with the rights of society be accurately defined and set forth. This conflict is particularly evident in such chronic infections as syphilis and tuberculosis, but arises, no less, in the treatment of other infectious diseases which require restrictive measures for the protection of society.

## PUBLIC HEALTH VERSUS CLINICAL IDEALS

In the case of tuberculosis this conflict is emphasized by the fact that the disease is long drawn out, is particularly prevalent among the families of working men, and goes hand in hand with low incomes and inadequate standards of living; and furthermore by the fact that in our present economic status from 70 to 90 per cent of tuberculous patients require public or private aid to enable them to secure the advantage of established treatment. Since most of the public sanatoria are under the jurisdiction of Departments of Health, this brings the treatment of most tuberculous patients under the care of physicians whose facilities for treatment are usually wholly inadequate for giving the best care to the individual, and whose training and practice lead them to recognize that the protection of society is paramount to the rights of the patient.

Where the prevention of the spread of infection is given greatest attention, the course followed may not always coincide with best clinical practice. Prevention is especially stressed among the poor because it is so much more necessary to protect the children in these families than in those of higher economic standards who live in a better environment and who are treated by private physicians. Treating those who receive public care presents the problem not only of devising methods which will as quickly as possible render them incapable of infecting others, but, the same as those who are more fortunate economically, the problem of restoring them to the greatest possible degree of future independence. This latter problem is often insufficiently considered in the desire to accomplish the first objective.

If the plan of treatment proves to be less favorable to the patient than that offered by the best clinical practice, the course is defended on the ground that the sacrifice which is made on the part of the individual will be compensated by the reduced danger of infection among those who associate with him, consequently in the lessened amount of disease in the next generation; and further by the fact that communities do not

have the necessary funds to provide the facilities for dealing with their tuberculosis problems in the most satisfactory manner. However, we must always bear in mind that hygienically treated patients who fail to secure a healing live much longer than those who are not the recipients of such care, and that this increases both the problem of prevention and the cost of care; so the only economy in treating tuberculosis is early diagnosis and immediate adequate treatment.

Under present practice communities meet their tuberculosis problems largely by yielding to the demands of Public Health and overruling to a certain extent the ideals of clinical practice. They are too often forced to allow public good to overshadow the rights of the individual; and expediency to determine the course to be pursued. The necessity of making expediency override clinical ideals cannot be eliminated until governments provide ample sanatoria and ample medical and nursing service for all patients who require community care. This might be done at a saving to the community if a program were devised which would insure the treatment of tuberculosis in its early stages; and at this time a much larger percentage of patients can be restored to usefulness by an expenditure of money far less in amount than that which is being expended on advanced cases to-day.

It is frequently said that artificial pneumothorax is the greatest advance that has been made in the treatment of tuberculosis. It is evident that: (*1*) More patients who suffer from advanced tuberculosis can be treated successfully with pneumothorax than by physiological principles alone; (*2*) patients' sputum may be rendered bacillus-free quicker by its use than by physiological principles alone; (*3*) more physicians are suited to the employment of such mechanical measures than to the daily routine of encouraging and guiding the patient so that he secures the benefit of a high physiological balance; (*4*) it gives the physician control over the patient as long as it is administered, which is frequently sufficiently long for healing to be brought about; (*5*) the patient is obliged to coöperate at least to the extent of returning for refills. It is equally evident that many patients who are treated by pneumothorax could secure a healing without it.

Every tuberculosis specialist to-day recognizes the value of compression in the treatment of tuberculosis, and finds it absolutely necessary at times to the healing of the disease. They differ, however, in their opinion as to when it is necessary. By not rushing into collapse therapy it is often found that patients who at first seem to require it heal without

it; and, on the other hand, we must also admit that certain ones who seem to be favorable for spontaneous healing fail to heal and must be aided later by some form of compression.

## EFFICACY OF PHYSIOLOGICAL MEASURES AND DIFFICULTY IN APPLYING THEM

Those who have been successful in carrying out physiological treatment by the usual hygienic-dietetic, open-air regimen realize how unimpressive it is, with its lack of spectacular appeal, how difficult it is to make the patient realize that nature will heal the lesion if he will live a restricted and directed life for a sufficient period of time. The patient is much more impressed by such operative procedures as injecting air or gas into the pleural cavity, crushing the phrenic nerve, intrapleural pneumonolysis and thoracoplasty.

Nevertheless, it is not tuberculosis that requires operative procedures so much for its healing as advanced tuberculosis; and, except when far advanced, it is not the disease that provides the problems of therapy so much as the patient. Proper guidance of the patient, no matter what therapy is used, will increase the number of favorable results; and proper after-care will make permanent many arrestments which, without it, will be followed by relapse.

The indications which are accepted as requiring compression to-day are too broad. They are present in many patients who may better be treated without it. In case a waiting period is established, to see if healing will take place without mechanical aid, it is often much shorter than is warranted by the known slowness with which pathological changes take place in clinical tuberculosis. The natural resistance of the patient, aided by the compensating mechanism with which he is normally provided, is sufficient to meet most of the demands of early lesions and many of the demands of more advanced disease. Where mechanical measures are to be employed, a temporary phrenic will often suffice; in which case the healing which follows is accomplished with little or no unnecessary permanent damage to the patient's respiratory mechanism. The efficacy of phrenic interruption is increased by keeping the patient in bed, with weights such as shot or sand-bags over the chest, following the operation. When these measures fail, pneumothorax, either with or without pneumonolysis, will often succeed. Probably because of our success in bringing serious cases to a successful issue, it is not sufficiently emphasized that the more advanced the

lesion the longer the required treatment; the greater the danger of complications; and likewise the greater the reduction in the patient's future efficiency. This has one very important meaning in a community program. It costs dollars, and many of them.

I sometimes wonder if we, as specialists, are not so impressed by the favorable results that may be obtained in advanced tuberculosis that we fail to grasp the seriousness of advanced disease and the serious consequences which often follow its treatment.

Empyemata, nonexpanded lungs, and extensive fibrosis with compensatory emphysema are the prices that many tuberculous patients pay, even though they recover from the disease; and a prolonged treatment, a prolonged life, an extended dependence and an increased danger of scattering infection is the price which the community pays for failing to treat the disease early. If early diagnoses were made and immediate treatment instituted, whether it be physiological measures alone or physiological measures supplemented by compression, there would be a minimum of lung injury and a maximum of favorable results at a great saving of time and expense. The medical profession as a whole can render as great a service to tuberculous patients as it has to those suffering from appendicitis by recognizing the disease in its early phases and seeing that proper therapeutic measures are immediately applied.

## THE USUAL METHOD OF DETERMINING WHEN PATIENTS ARE BACILLUS-FREE IS UNSATISFACTORY

It is frequently stated that by compressing the lung we quickly render patients bacillus-free. Until we know how many of these patients whom we are treating so vigorously to-day will be restored to permanent economic independence, we cannot be sure of the efficacy of our program.

The Ziehl-Neelsen method of examining sputum is recognized as inadequate as a basis for declaring a patient bacillus-free. It requires the presence of about 100,000 bacilli per cubic centimetre of material examined for the specimen to be positive by direct smear (Corper). Consequently patients carrying less bacilli than this number would not yield a positive microscopical result by the old method.

We have had recourse to the dilution-flotation method, which is a refinement of the well known concentration techniques in which hydrocarbons are employed. This method with picric acid as counterstain has been demonstrated by quantitative methods to be approximately seventy-five times more sensitive than the direct smear made

from likely particles, where methylene-blue is used as a counterstain. This would reduce the number of bacilli demonstrable by the microscope to a little over 1,000 per cubic centimetre. Beyond this it is necessary to employ a guinea pig or culture methods in order to make a diagnosis.

The dilution-flotation method has been used in our institution for twenty-three years as a routine procedure. We have noticed that we were not able to get our patients who were doing well free from bacilli in as high a percentage as had been reported by others. A tabulation of patients shows that less than five per cent of those who enter with bacilli pass the flotation test successfully, while under treatment. In a further tabulation of 1,700 separate examinations, all of which were positive by the dilution-flotation method, only about one-fifth would likely be positive by direct smear.

The inaccuracy of the usual methods of determining when a patient is no longer casting off bacilli has given a wrong interpretation of results obtained under treatment and has probably blinded us to the true cause of relapse in certain patients who had been pronounced arrested. The fact is that many of these patients who have been discharged from treatment after a few months with supposedly negative sputum were still shedding bacilli; some probably daily, others every few days, some only every few weeks, and still others only under extraordinary conditions such as following a cold or bronchitis. Our experience demonstrates that patients may be bacillus-free for three or six months on three-day specimens and then have them reappear for a time, and repeat the process of disappearing and reappearing, yet all the time the patient is improving in a satisfactory manner. Furthermore, it is impossible at times to determine the point in the lung from which bacilli come. They may come from the contralateral lung when the lung with the most severe lesion has been compressed.

### A LONG PERIOD OF TREATMENT BEST PREVENTIVE OF RELAPSE

A decided advantage in pneumothorax treatment as compared with hygienic measures alone, lies in the fact that treatment is carried on longer, it is not uncommon to keep a lung compressed for three or four years. In patients who are favorable for cure under nonoperative measures I rarely find it necessary for even the advanced ones to carry out a strict regimen for more than eighteen months or two years; and the latter portion of this time is used in preparing them to resume work. I supplement the intensive treatment when they are resuming work

by a modified regimen during the first two or three years following discharge. This consists of much rest and an adequate amount of walking, the principle consisting of having the patient live within his daily store of energy and do the things which will keep up his strength.

Frequent relapse is one of the most disappointing features of the treatment of tuberculosis. The cause can mostly be found in inadequate treatment, and a return to unfavorable environment with the resumption of a too strenuous life. We find that very few of our patients who are treated in the above manner suffer relapse of their disease; and furthermore, most of those with rare bacilli eventually become bacillus-free.

The greatest advances in the future treatment of tuberculosis should come through its early recognition and immediate treatment. The tendency to heal is strong in most cases as long as the pulmonary tissues are elastic and capable of compensating.

There are two main questions which determine the prognosis in a given case of tuberculosis: one local; the other general. The local factor is the ability of the pulmonary tissues and the enveloping structures to compensate for the loss of tissue by lessening the size of the thoracic cage and by a compensatory enlargement of air cells on the part of the lung, so as to maintain a proper equilibrium between the size of the thoracic cavity and the contracting lung. This compensating mechanism is the one which collapse measures imitate. The general factor is the patient's physiological equilibrium. Remembering that healing is a physiological process, it is necessary to maintain the highest possible state of physiological activity on the part of the patient while healing is going on. It is around these two factors that an adequate therapy in tuberculosis, either knowingly or unknowingly, has always been built.

Early methods of treating tuberculosis were based wholly on an attempt to improve the general physiological state of the patient; and they proved sufficiently successful to establish the curability of tuberculosis. This applied even in matters immunological, because immunological reactions have a physiological basis. However, the failures in these early attempts were many, especially in the later stages of the disease when mechanical hindrances are prominent. The methods of treatment which have been devised more recently have been directed largely toward overcoming the mechanical hindrances which interfere with healing; often, too, with neglect of the physiological factors.

Because compression is successful in early cases and also in many

of the later and more advanced ones where there is little hope of successful treatment without it, there is a tendency on the part of many clinicians to disregard or underestimate the results that may be obtained by utilizing the patient's own physiological forces in treating cases which present no serious mechanical factors. Some of the most brilliant results in the application of pneumothorax have been obtained in early exudative lesions without widespread adhesions which have been responding to the hygienic-physiological regimen since Brehmer's time.

### EXPEDIENCY SHOULD NOT BE SO PROMINENT A FACTOR IN THE TREATMENT OF THE FUTURE

We now have much of the necessary information at hand to determine more carefully than we have been doing the cases of tuberculosis which will heal with physiological measures alone and those which require surgical aid. Our opinion of the treatment which is to be employed, however, is always subject to modification by the circumstances under which treatment will be carried out. In order to be accurate in our estimate of these methods, we should differentiate between measures of necessity and measures of expediency. Because a patient can sometimes be better controlled by compression, and because compressing a freshly formed exudate and cavity results in healing, must not be interpreted as meaning that these conditions of necessity call for compression. It goes without saying that if all patients could be treated ideally, that is, early and under ideal circumstances, and could be depended upon for a whole-hearted coöperation, compression would rarely be found necessary to the actual healing of their lesions. However, this does not imply that expedience would not demand that many such cases be compressed.

While expediency must, at the present time, dominate the treatment of those who fall under the Public Health branch of medicine, if for no other reason than the inadequacy of facilities for treatment, it should require no discussion to establish the right of each patient whenever possible to secure that treatment which is best suited to restore him to health and at the same time to enable him to secure the greatest degree of efficiency commensurate with the pulmonary involvement present.

Not only immediate results but the permanency of results depends much upon the economic and social status of the patient. He who can return to a well regulated home, with pleasant surroundings and good food, has a great advantage in his future course. Few patients remain

in institutions long enough for cure to be accomplished. Their future depends much upon whether they can continue to live under conditions similar to those in institutions or whether they must go back to unhygienic conditions and unfavorable environments. These facts must always be considered when choosing the type of treatment which shall be instituted in a given case. The treatment of tuberculosis, whenever possible, should be dominated by the best possible accomplishments of clinical medicine, but expediency, on the other hand, at times is the only factor capable of producing a result.

In recent times the political aspects of tuberculosis have become of tremendous importance. Governments have been forced by advances in the scientific understanding of both the clinical and preventive phases of tuberculosis to provide large sums of money for prevention and cure; sums, however, which still fall far short of being adequate. Laws have been passed establishing hygienic conditions in workshops and homes that infection may be reduced to a minimum, and that those who are ill may be better cared for. Organizations are also seeking out the infected and providing treatment for those who require it. Thus science has called upon society to spend millions of dollars that posterity may escape the ravages of tuberculosis. It is up to medicine to see that this money is spent wisely, and that the best interests of both patient and society are conserved.

# POSITIVE INTRAPLEURAL PRESSURE AS AN AID TO PNEUMOTHORAX THERAPY[1]

GEOFFREY EDSALL[2]

The use of positive intrapleural pressure as an adjunct to simple pneumothorax is a procedure of long standing. While it is recognized that there are cases in which an incomplete collapse, an unhealed cavity, or a stubbornly positive sputum may be remedied or benefited by compression of the lung, there are many phthisiologists who doubt that the procedure is safe and effective enough to be more than rarely justified. Furthermore, various other manoeuvres, such as intrapleural pneumonolysis, have more recently been devised to remedy the circumstances formerly met by the use of increased pressure. The latter nevertheless remains the only nonoperative technique in general use at present, and this alone would justify an inquiry into its merits.

Very few observations on the subject are available. Dunham (1) in 1928 reported favorably on the use of high intrapleural pressures (10 cm. of water, or higher) in patients with pleural adhesions; he presented six cases showing good results. Amberson and his associates (2) have found that mild positive pressures (from plus 2 to plus 6 or 8), if kept relatively uniform by frequent refills, are often very useful for stretching small adhesions. They observed no increase in the incidence of complications, but they have not found the method effective in the healing of cavities where broad adhesions are present. Genevrier and Descomps (3), in a study of the mechanism of pulmonary collapse, conclude that pressures greater than neutral can only be harmful, since they believe that attempts to stretch adhesions or to compress cavities usually only shift the mediastinum and compress the healthier lung. Likewise Lefèvre and Delannoy (4), in advocating "expiratory zero" as an optimum pressure end point, state that "the use of positive pressures (in expiration), rather than augmenting the static repose of the lesions, will on the contrary result in augmenting the dynamic traumatism which they will suffer." Their conclusions, however, appear to be wholly

[1] From the Trudeau Sanatorium, Trudeau, New York.
[2] Cambridge, Massachusetts.

theoretical, and they give no consideration to the effects of increased pressure upon adhesions or cavities.

The standard textbooks on pneumothorax give scant attention to positive pressure therapy. Riviere (5) states simply that adherent bands "may often be stretched or divided under refills of gas rapidly repeated, with a rising but moderate pressure. This method is without danger in skilled hands." And he remarks later that "small positive pressures (plus 3 to plus 10, mean) are generally sufficient to maintain collapse." But he quotes Saugman as commenting favorably on the use of pressures as high as 30 to 40 cm. water. Dumarest (6) states that in cases with adhesions "it has been necessary to employ relatively elevated pressures (plus 11 to plus 16) in order to put the lung into a state of sufficient compression." Fischer (7), in a recent briefer manual on the subject, gives no consideration to increased pressures, except as involving risks when rapidly induced.

Since no detailed studies of the subject were to be found in the literature, an analysis was made of the pneumothorax treatments administered at Trudeau Sanatorium during the years 1929 to 1933 inclusive. From a total of about 275 cases receiving pneumothorax, 68 were found in which, at some time during their stay, intrapleural pressures above zero on inspiration had been recorded. The standard of positive pressure thus selected is debatable, but, in the absence of general agreement upon the definition of such pressure, it was decided to include for consideration all cases in which the pressure had remained positive throughout the respiratory cycle for more than occasional refills. Of the 68 cases thus selected, 6 had received positive pressures too irregularly for consideration, 7 had developed at best only a pocket pneumothorax, and 12 developed positive pressure spontaneously, as a result of effusion or of bronchopleural fistula. Hence 43 cases remained, in which positive pressures to a significant degree were induced artificially and were sustained over several refills. All such cases were regarded as suitable for consideration of the *incidence of complications* associated with positive pressure; but in only 30 of the cases were there data adequate for *comparing the effects* of normal versus positive pressure.

The reasons for employing positive pressure were sought in the records of the 30 cases wherein this treatment was applied after a control period on normal pressure. In 29 cases reasons were indicated as follows (in five cases more than one reason appeared):

(1) For adhesions, or ineffective collapse..... 18
(2) For persistent cavity..... 12
(3) For persistently positive sputum..... 4

Significant adhesions were observed by X-ray, however, in all but three of these cases, so that it seems justifiable to assume that the usual reason for changing the pressure was the need for improving a collapse rendered inadequate by the presence of pleural adhesions.

In seeking an evaluation of the results obtained with the use of positive pressure, it was found practical to consider the cases from the following standpoints: (*1*) effect on degree of collapse; (*2*) effect on Gaffky count; (*3*) effect on healing of cavities; (*4*) general results; and (*5*) complications. These questions are considered in detail below.

(*1*) *Effect on degree of collapse:* Following the percentage method of estimate employed at Trudeau, the increases in collapse observed following raised pressure were: (*a*) over 15 per cent in 15 cases, average pressure 5.25 cm. water; (*b*) 10 to 15 per cent in 9 cases, average pressure 5.75 cm. water; and (*c*) less than 10 per cent in 6 cases, average pressure 5.6 cm. water. The increases for the entire group averaged 17 per cent.

Above are given the average pressures obtained in each group. These were calculated in order to determine whether results were consistently related to the pressure employed. It is apparent that such is not the case.

(*2*) *Effect on Gaffky count:* In considering this question and the next one below, it was felt that cases afforded data suitable for comparison only if they exhibited readings for normal and positive pressures for at least two months each, and if they showed no signs of improvement during the two months preceding the commencement of positive pressure. In 17 such cases: 2 became Gaffky zero within two months, 7 showed a trend to a lower average Gaffky count, 6 remained essentially unchanged, and 2 became worse.

(*3*) *Healing of cavities* could be compared in 13 cases, of which, under positive pressure, 10 showed definite acceleration of healing, 2 remained essentially unchanged, and 1 became worse (maximum collapse was 60 per cent).

(*4*) *General results* were regarded as good if the case, while under positive pressure, showed either an increase of over 15 per cent in collapse, a definite improvement in the healing of a cavity, or a definite decrease in the Gaffky count, provided that during the period in question the

condition of the patient in no respect became worse. The cases were grouped as follows:

| | |
|---|---|
| (1) Definite improvement | 14 |
| (2) Improvement on positive pressure, relapse on lowered pressure | 2 |
| (3) Slight or questionable improvement | 5 |
| (4) No change | 3 |
| (5) Worse | 4 |
| (6) Pressure increase poorly tolerated | 2 |

Thus approximately half of the group (14 out of 30 cases) seemed to derive definite benefit from the increased pressure, and 7 more cases may have benefited to some extent. On the other hand, the 8 cases in groups 2, 5 and 6, representing difficulties in treatment, are of especial interest, and are therefore considered in detail.

(5) *Complications:* In two patients severe dyspnoea required abandonment of higher pressures; one of these subsequently developed infiltration of the contralateral lung. Another developed a similar extension while under positive pressure. In one case a cavity expanded while under positive pressure (see section 3 above), while in another a cavity appeared only after abandonment of an apparently satisfactory pressure increase. Two patients showed temporary benefit following the elevation of pressure, only to relapse with extensive effusions and a rising Gaffky count. Another patient developed a cavity, after a good collapse under positive pressure (85 per cent) had receded to 65 per cent. It is worth noting that, of the four patients relapsing under higher pressures, three never had more than a 70 per cent collapse.

Among the 13 cases not subject to comparative analysis, two major complications occurred subsequent to the induction of positive pressure. One patient developed a bronchopleural fistula, following an emergency collapse for haemoptysis. Another died of tuberculous empyema; he had received minimal positive pressures for six weeks, returning to normal pressure six weeks or more before the first signs of effusion appeared.

Fluid was apparently responsible for the occurrence of *spontaneous* positive pressure in 10 of the 68 cases. Among the 30 cases subject to comparative study, the occurrence of fluid was as follows:

| | |
|---|---|
| (1) No fluid while under pneumothorax treatment | 12 |
| (2) Fluid appeared before rise in pressure | 10 |
| (3) Fluid appeared during positive pressure | 4 |
| (4) Fluid appeared after return to normal pressure | 4 |

Thus serious complications occurred in about one-seventh of the patients considered; the complications usually anticipated as a consequence of positive pressure (massive effusion, empyema, fistula) arose with comparative infrequency.

## DISCUSSION

In the cases here presented, positive pressure was employed as an adjunct to simple pneumothorax, after the latter alone had proved therapeutically unsatisfactory. The question at hand is: Can the procedure be said to have justified itself? While the series of cases here discussed is small, there are nevertheless sufficient data to warrant an attempt at reaching conclusions. On the one hand, it has appeared that positive pressure was beneficial in one-half, or perhaps more, of the cases in which it was tried. This is particularly significant, in view of the facts that the average pressure employed was only 5.5 cm. water, and that in only 9 cases were pressures averaging more than 9 cm. applied. On the other hand, complications arose in about one-seventh of the cases. While it is impossible to determine the influence of positive pressure in the onset of each complication, it cannot be denied that such increases *may* be directly followed by extension, effusion, empyema or rupture of the lung. Such events, however, were quite rare in this series, and the experience of Amberson and of Riviere has evidently been similar. Moreover, though a slight risk of complications may be incurred under positive pressure, the benefits that may be obtained are of great importance. Many cases of simple pneumothorax cannot obtain a collapse sufficient to produce adequate healing, and it frequently turns out that such a pneumothorax is worse than none at all. Numerous investigations, such as those recently reported by Bentley (8), have statistically confirmed the importance of obtaining complete collapse. In the present series, 11 patients obtained 90 per cent collapse or more only after the induction of positive pressure, and in several other cases a previously ineffective collapse was rendered effective, even though not complete, by a rise in intrapleural pressure. One cannot overlook the great value of such operative procedures as intrapleural pneumonolysis, which in recent years have often relieved difficulties formerly attacked less effectively by positive pressure. But there still remain many patients in whom the simpler procedure may accomplish the desired result. There were in fact two patients in the present series who improved on positive pressure after pneumonolysis had proved

unsatisfactory. In view of the considerations described, then, it seems reasonable to conclude that positive pressure pneumothorax has a definite (though limited) place in the treatment of patients having an inadequate collapse because of adhesions.

The results obtained with cavities would be impressive, if the group were not obviously too small to merit conclusions. The changes produced in the Gaffky count are disappointing, since positive pressure is not infrequently applied in the hope of converting a positive to a negative sputum. Rapid changes in the sputum are seen as a rule, however, in early cases with relatively little chronic inflammation, and such cases are not as a rule submitted to increased pressure.

In general, it would seem that any dispute regarding the safety and efficacy of positive pressure therapy may be based largely upon differences in selection of cases, or in technique. While there is no doubt that positive pressures rapidly induced, or raised to an unduly high level, may produce disaster, there is on the other hand adequate evidence that slowly increased pressures of moderate degree, kept fairly uniform by small frequent refills, will incur little if any extra risk. And finally, while one cannot expect positive pressure to overcome the impediment of massive adhesions, it has often been noted that such pressure may stretch a smaller adhesion, and thereby render a collapse effective. Thus the results obtained by the use of positive pressure depend to a very large extent upon care in two primary considerations—selection of cases, and control of the technique.

## SUMMARY

1. Sixty-eight patients, or one-fourth of the total receiving artificial pneumothorax during the period 1929 to 1933 inclusive, exhibited positive pressure at some time during their treatment at Trudeau Sanatorium.

2. In 43 of these patients, significant positive pressures were induced artificially, and sustained for several refills. Thirty of these patients received both normal and positive pressures for intervals suitable for comparison.

3. Analysis of the records of these 30 cases showed that:

(*a*) Positive pressure was usually employed to improve a collapse rendered inadequate under normal pressures because of pleural adhesions.

(*b*) Positive pressure in 15 cases produced an increase in collapse of over 15 per cent; the average increase in 30 cases was 17 per cent.

The increase obtained was not consistently related to the pressure employed.

(*c*) In 13 cases healing of cavities under both types of pressure could be compared. Ten cases showed accelerated healing while under positive pressure.

(*d*) In 17 cases with previously unimproved Gaffky counts, induction of positive pressure was followed within two months by a negative sputum in two cases, and a lowered Gaffky count in 7 other cases.

(*e*) General results following positive pressure were definitely good in 14 out of the 30 cases, and possibly beneficial in 7 others.

(*f*) Complications possibly related to the use of positive pressure occurred in 4 of the 30 cases. In the 13 cases, wherein pressure effects were not comparable, two major complications occurred subsequent to the induction of positive pressure.

4. The judicious and careful application of moderate positive pressure is a worth while procedure in selected cases where simple pneumothorax has failed to produce satisfactory collapse and healing of the lung.

## REFERENCES

(1) Dunham, R. W.: Illinois Med. Jour., 1928, *54*, 267.
(2) Amberson, J. B., Jr.: Personal communication.
(3) Genevrier, J., and Descomps, H.: Presse méd., 1929, *37*, 652.
(4) Lefèvre, J., and Delannoy, J.: Ibid., 1935, *43*, 1048.
(5) Riviere, C.: Pneumothorax and surgical treatment of pulmonary tuberculosis, Oxford Univ. Press, Oxford, 1928.
(6) Dumarest, F., and Brette, P.: La Pratique du pneumothorax thérapeutique, ed. 2, Masson & Cie., Paris, 1923.
(7) Fischer, A.: Pneumothoraxtherapie in der täglichen Praxis, Weidmann, Vienna, 1935.
(8) Bentley, F. J.: Med. Research Council, Special Report no. 215, His Majesty's Stationer's Office, London, 1936.

# TUBERCULOUS INFECTION IN NEGRO COLLEGES[1]

PAUL B. CORNELY AND E. H. ALLEN

The tuberculosis death rate for Negroes of all ages in the United States is, as has often been stated, from two to three times that of the white population. This inequality, however, is greatest in the younger ages. In 1930, the rate for the male Negro between the ages of 15 and 19 was 7.1 times that of the white in the same age group, while the ratio of colored to white death rate in young women, 10 to 14 years of age, was 8.6 to 1 (1). Between the ages of 15 and 44, tuberculosis is still the first cause of death for both racial groups. Therefore, the necessity for continuous vigilance in this age group, particularly in the Negro, is obvious.

It is now recognized that the college is an important strategic place for attack on this disease. During the past five years, through the activities of the Tuberculosis Committee of the American Student Health Association (2), white colleges and universities have yearly devoted more and more time to this problem. On the other hand, except for a report by Scott (3) on the tuberculosis program being developed at Hampton Institute, very little has been said about this work in Negro institutions. In order to determine the extent of tuberculosis case-finding programs in these colleges, questionnaires were sent to 104 collegiate institutions requesting information on the extent and results of tuberculin-testing of their students for the school years 1933–1934 through 1936–1937. Thirty-five institutions with an enrollment of 14,162, approximately 50 per cent of the total attendance in Negro colleges in the United States, responded.

Table 1 shows that group tuberculin-testing is not common in Negro schools. Only one institution, as shown in table 2, has done tuberculin-testing on entering students for three consecutive years; 2 for two years, while three began this practice during the past school year. The other 5 institutions have done the test irregularly or only in suspicious cases. Of the 11 schools, 8 stated that X-rays of reactors were taken.

[1] From the Department of Bacteriology, Preventive Medicine and Public Health, and the Department of Student Health Service, Howard University Medical School, Washington, D. C.

## INCIDENCE OF TUBERCULOSIS INFECTION

The incidence of tuberculosis infection in a group is measured by the percentage of positive reactors. Obviously, it is very difficult at present to accurately estimate this for the 25,000 Negro college students. However, certain available data give a suggestion as to the prevalence of tuberculosis exposure among Negro college students. In tables 2 and 3, based on information from the questionnaires, it is seen that of 3,542 students in eleven institutions tested during 3 years, 33.9 per cent gave

TABLE 1

*Number of Negro colleges which reported a tuberculin-testing program, 1933–1936*

| ATTENDANCE | SCHOOLS REPORTING | NUMBER REPORTING TUBERCULIN-TESTING PROGRAM | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1933–1934 | | 1934–1935 | | 1935–1936 | | 1936–1937 | |
| | | Number reporting | Number tested | Number reporting | Number tested | Number reporting | Number tested | Number reporting | Number tested |
| Under 100 | 3 | | | | | | | 1 | 44 |
| 100–299 | 14 | | | | | 2 | 372 | 2 | 156 |
| 300–499 | 8 | | | | | 1 | 278 | 2 | 598 |
| 500 and over | 10 | | | 2 | 309 | 2 | 949 | 3 | 836 |
| Total | 35 | | | 2 | 309 | 5 | 1,599 | 8 | 1,634 |

TABLE 2

*Results of tuberculin-testing in different Negro colleges, 1933–1936*

| INSTITUTIONS | 1934–1935 | | 1935–1936 | | 1936–1937 | |
|---|---|---|---|---|---|---|
| | Number tested | Per cent positive | Number tested | Per cent positive | Number tested | Per cent positive |
| All colleges | 309 | 26.9 | 1,599 | 27.6 | 1,634 | 41.4 |
| Colored Agricultural and Normal University | 183 | 33.3 | | | | |
| A. and T. of N. C. | 126 | 17.5 | 600 | 23.5 | 301 | 30.9 |
| W. Va. State College | | | 349 | 35.8 | | |
| Alcorn A. and M., Alcorn, Miss. | | | 278 | 33.1 | 170 | 50.6 |
| Tillotson | | | 132 | 18.2 | 50 | 25.0 |
| Knoxville College, Knoxville, Tenn. | | | 240 | 25.0 | | |
| Shaw University, Raleigh, N. C. | | | | | 428 | 44.8 |
| Elizabeth City State Normal School | | | | | 515 | 41.2 |
| Talladega | | | | | 6 | 0 |
| Gammon Theological Seminary, Atlanta, Ga. | | | | | 44 | 63.6 |
| Howard University, Washington, D. C. | | | | | 120 | 45.0 |

a positive reaction. Incidentally, it is also observed that the incidence of reactors varied from one institution to another, and in the same school from one year to the other.

In the summer of 1935, the National Tuberculosis Association made available PPD free of charge to those Negro colleges and universities which were willing to carry out complete tests and send their results to the Association for compilation. Eight Negro colleges took advantage of this offer. The colleges and their location are shown in table 4.

TABLE 3

*Total results of tuberculin-testing in Negro colleges, 1933–1936*

| SCHOOL YEAR | SCHOOLS REPORTING PROGRAM | NUMBER TESTED | PER CENT POSITIVE |
|---|---|---|---|
| 1933–1934 | | | |
| 1934–1935 | 2 | 309 | 26.9 |
| 1935–1936 | 5 | 1,599 | 27.6 |
| 1936–1937 | 8 | 1,634 | 41.4 |
| Total..... | 15 | 3,542 | 33.9 |

TABLE 4

*Negro institutions in which tuberculin tests were made with PPD*

| INSTITUTION | STATE | NUMBER TESTED |
|---|---|---|
| Paine College | Georgia | 238 |
| Agricultural, Mechanical and Normal College | Arkansas | 322 |
| Alcorn A. and M. College | Mississippi | 278 |
| Wilberforce University | Ohio | 372 |
| Storer College | West Virginia | 93 |
| Maryland Normal College | Maryland | 120 |
| Virginia State College for Negroes | Virginia | 840 |
| West Virginia State College | West Virginia | 300 |

Miss Jessamine Whitney, of the National Tuberculosis Association, kindly sent us the analysis and tabulation of the results of the 2,040 students tested. These data are reproduced in tables 5 and 6. It is noticed that for all ages the percentage of positive reactors is 39.1. As would be expected, reactors gradually increase with age. There is also a marked difference between the two sexes. For all ages, the percentage of positive reactors was 44.0 for the male, and 35.4 for the female, a difference of approximately 10 per cent. This is true for

practically each year considered. This disparity between the sexes has already been noted in white students (4, 5); however, the inequality seems to be more marked in the Negro.

TABLE 5

*Results of tuberculin-testing with PPD in eight Negro colleges in 1935–1936*

Male

| AGE | NUMBER GIVEN FIRST TEST | PER CENT POSITIVE TO FIRST TEST | NUMBER GIVEN SECOND TEST | PER CENT POSITIVE TO SECOND TEST | TOTAL PER CENT POSITIVE |
|---|---|---|---|---|---|
| All ages | 886 | 36.0 | 396 | 17.9 | 44.0 |
| 15 | 1 | | 1 | | |
| 16 | 4 | | 4 | 25.0 | 25.0 |
| 17 | 24 | 25.0 | 12 | 16.7 | 33.3 |
| 18 | 67 | 32.8 | 32 | 15.6 | 40.3 |
| 19 | 119 | 29.4 | 56 | 12.5 | 35.3 |
| 20 | 156 | 37.8 | 67 | 16.4 | 44.9 |
| 21 | 149 | 32.9 | 68 | 17.6 | 40.0 |
| 22 | 124 | 37.9 | 60 | 20.0 | 47.6 |
| 23 | 90 | 37.8 | 38 | 18.4 | 45.6 |
| 24 | 44 | 40.9 | 22 | 18.2 | 50.0 |
| 25 | 39 | 53.8 | 12 | 41.7 | 66.7 |
| 26 | 22 | 50.0 | 10 | 20.0 | 59.1 |
| 27 | 16 | 43.8 | 6 | 16.7 | 50.0 |
| 28 | 6 | 33.3 | 1 | | 33.3 |
| 29 | 4 | 50.0 | 1 | 100.0 | 75.0 |
| 30 and over | 10 | 20.0 | 5 | 20.0 | 30.0 |
| Age unknown | 11 | 36.4 | 1 | | 36.4 |
| Freshmen | 350 | 32.0 | 153 | 18.3 | 40.0 |
| Sophomores | 197 | 38.6 | 90 | 15.6 | 45.7 |
| Juniors | 167 | 41.3 | 77 | 16.9 | 49.1 |
| Seniors | 142 | 40.1 | 63 | 23.8 | 50.7 |
| Special | 10 | 50.0 | 3 | | 50.0 |
| No report | 20 | | 10 | 10.0 | 5.0 |

The last tuberculin-testing survey to be considered is that of the Extension Department of the North Carolina Sanatorium. Under the direction of Dr. P. P. McCain, 9,149 college students, of whom 2,538 were Negroes, have been tested in recent years with 0.1 mgm. of Old Tuberculin intracutaneously. The performance and interpretation of the test, unlike the other two surveys, were made by an experi-

TABLE 6

*Results of tuberculin-testing with PPD in eight Negro colleges in 1935–1936*

Female

| AGE | NUMBER GIVEN FIRST TEST | PER CENT POSITIVE TO FIRST TEST | NUMBER GIVEN SECOND TEST | PER CENT POSITIVE TO SECOND TEST | TOTAL PER CENT POSITIVE |
|---|---|---|---|---|---|
| All ages | 1,154 | 27.9 | 496 | 17.3 | 25.4 |
| 15 | 4 | 25.0 | 1 | | 25.0 |
| 16 | 31 | 9.7 | 20 | 20.0 | 22.6 |
| 17 | 86 | 18.6 | 41 | 12.2 | 24.4 |
| 18 | 187 | 26.2 | 83 | 12.0 | 31.6 |
| 19 | 221 | 29.0 | 92 | 12.0 | 33.9 |
| 20 | 216 | 25.0 | 89 | 19.1 | 32.9 |
| 21 | 170 | 31.8 | 71 | 25.4 | 42.4 |
| 22 | 90 | 35.6 | 31 | 12.9 | 40.0 |
| 23 | 56 | 25.0 | 26 | 11.5 | 30.4 |
| 24 | 27 | 18.5 | 19 | 10.5 | 25.9 |
| 25 | 18 | 22.2 | 11 | 18.2 | 33.3 |
| 26 | 9 | 55.6 | 2 | 50.0 | 66.7 |
| 27 | 7 | 85.7 | 1 | 100.0 | 100.0 |
| 28 | 7 | | 4 | 100.0 | 57.1 |
| 29 | 3 | 66.7 | | | 66.7 |
| 30 and over | 14 | 64.3 | 3 | 100.0 | 85.7 |
| Age unknown | 8 | 50.0 | 2 | 50.0 | 62.5 |
| Freshmen | 456 | 29.4 | 200 | 18.0 | 37.3 |
| Sophomores | 277 | 24.0 | 133 | 19.5 | 34.3 |
| Juniors | 184 | 32.1 | 80 | 17.5 | 39.7 |
| Seniors | 168 | 33.3 | 46 | 19.6 | 38.7 |
| Special | 8 | 50.0 | 1 | 100.0 | 62.5 |
| No report | 61 | | 36 | | |

TABLE 7

*Report of tuberculin tests of 9,149 North Carolina College students (0.1 mgm. Old Tuberculin intracutaneously)*

| | NUMBER TESTED | NUMBER OF REACTORS | PERCENTAGE OF REACTORS |
|---|---|---|---|
| White | 6,611 | 2,071 | 31.02 |
| Colored | 2,538 | 1,119 | 48.02 |
| Total | 9,149 | 3,190 | 34.80 |

enced clinic physician from the North Carolina Sanatorium. In table 7 (6) it is noted that the percentage of reactors in this group is 48.0. This figure is much higher than those of the two aforementioned studies. The explanation for this disparity is not clear at present. It would be of interest to know something about the sex and age distribution of the subjects of this study. Of significance also is the fact that, although there is a great disparity between the percentage of white and Negro positive reactors, the X-ray findings of the two groups do not show these differences. This is well shown in table 8 (6).

TABLE 8

*Result of X-ray study of 2,770 reactors among North Carolina students*

| | NUMBER HAVING X-RAYS | ADULT-TYPE TUBERCULOSIS | | | CHILDHOOD-TYPE TUBERCULOSIS | | |
|---|---|---|---|---|---|---|---|
| | | Number | Per cent of number tested | Per cent of number X-rayed | Number | Per cent of number tested | Per cent of number X-rayed |
| White | 1,799 | 42 | 0.63 | 2.6 | 216 | 3.2 | 13.8 |
| Negroes | 980 | 22 | 0.86 | 2.2 | 93 | 3.6 | 9.4 |
| Total | 2,779 | 64 | 0.69 | 2.5 | 309 | 3.3 | 12.1 |

## COMPARISON BETWEEN WHITE AND NEGRO STUDENTS

Accumulation of data from various white universities has shown that relatively high rates (from 40 to 60 per cent) are found in the colleges in the East and Far West, and low rates (from 20 to 30 per cent) in the Central States (4). The data for white Southern colleges, although extremely meagre, seem to show that the percentage falls between 30 and 40 (5, 7). This range for Southern colleges is substantiated by the data for the general population reported by Whitney and McCaffrey (8) which give the percentage of positive reactors for the South Atlantic, East South Central, and West South Central States, as 39.3, 33.1 and 23.4 respectively. Comparing this with the data from Negro colleges which for the most part are located in the South, the impression is derived that although the percentage of positive reactors in the Negro student group is higher, the difference is not as marked as would be expected in view of the higher morbidity and mortality.

The small difference in positive reactors between the white and Negro college students has been said to be due to the fact that Negroes in colleges come from houses where the environmental, social, economic

and educational advantages are the best. This, however, does not seem to be the proper explanation.

This same small difference in percentages has been found in grammar school where there is less selectivity (6). It has also been noted in the general population as shown by Whitney and McCaffrey. In our opinion, no explanation can be given at the present time. It must be remembered that the number of individuals who have been tuberculin-tested is still small. Many factors must be investigated before an adequate explanation can be given.

## SUMMARY AND CONCLUSION

Although the death rate from tuberculosis is higher in the Negro than in the white population, particularly in the younger ages, little effort is being made to develop tuberculosis case-finding programs in Negro colleges. Only 6 of 35 colleges are doing tuberculin-testing on entering students regularly, and only one has done this for the past three consecutive years. The dearth of this activity is intimately associated with the lack of student health activities in Negro colleges.

Available data seem to show that there is not much difference between the percentage of positive reactors in Negro and white college students. This seems to hold true in grammar schools and the general population. However, more extensive and uniform data are needed in this field before this can be positively stated.

## REFERENCES

(1) Whitney, Jessamine S.: New and supplementary facts and figures about tuberculosis, National Tuberculosis Association, 1935, p. 16.

(2) Fifth Annual Report of the Tuberculosis Committee of the American Student Health Association, Jour. Lancet, 1936, *56*, 492.

(3) Scott, C. W.: Tuberculosis program in Hampton Institute, Southern Workman, 1934, *63*, 298.

(4) Long, E. R., and Seibert, Florence B.: Tuberculous infection in American college students, Jour. Amer. Med. Assn., 1937, *108*, 1761.

(5) Shepard, C. E.: Campaign against tuberculosis in college students, Amer. Jour. Pub. Health, 1935, *25*, 1118.

(6) McCain, P. P.: The early diagnosis of tuberculosis with especial reference to the Negro. (Presented at the Amer. Sanatorium Assn., June, 1937. Copy of paper sent to authors.)

(7) Long, E. R.: Tuberculosis in college students with special reference to tuberculin, Jour. Lancet, 1935, *55*, 201.

(8) Whitney, J. S., and McCaffrey, I.: A summary of the results of group tuberculin-testing with P.P.D. in the United States, Amer. Rev. Tuberc., 1937, *35*, 597.

# A STUDY OF THE RESULTS OF TREATMENT OF PULMONARY TUBERCULOSIS IN MEXICAN AND WHITE PATIENTS[1]

FRED R. HARPER[2]

Considerable controversy has recently arisen over the type and severity of tuberculosis in Mexican compared with white patients. Rodriguez Pastor analyzed the results of two comprehensive studies made in Puerto Rico. He found that in neither study was any difference demonstrated between the forms of tuberculosis found among white and mulatto patients in Puerto Rico and that which is seen among white adults in the United States.

Alarcón was unable to find any special anatomicoclinical features nor increased severity of tuberculosis among Indians and Mestizos as compared with that seen in white people. He attributed the great tuberculosis mortality among Mexicans living in the United States to five causes: (*1*) extreme poverty among immigrants, (*2*) exceedingly bad housing, (*3*) lack of health education, (*4*) their position as foreigners and (*5*) dangerous trades in which they work.

Pinner feels that it is possible that adverse living conditions bring into clear manifestation some genotypic differences that remain hidden when the same people live under conditions that are for them normal by virtue of habituation and therefore adequate.

Reports from this country describe a distinct form of tuberculosis which is found primarily in Negroes, Mexicans and Puerto Ricans. Grethmann calls this form of tuberculosis "protracted haematogenous multiform tuberculosis." Grethmann describes the pulmonary lesions as being polymorphic and irregular without uniformity of distribution and lesions appearing and disappearing at intervals. In this form of haematogenous tuberculosis involvement of the lymph nodes and serous cavities is common. Also tuberculosis of other organs of the body frequently complicates the picture.

One of the most characteristic features of these nonmiliary types of

[1] From the Southern Pacific Railroad Sanatorium, Tucson, Arizona.
[2] Denver, Colorado.

haematogenous tuberculosis is the frequent association of extrapulmonary lesions. Reisner found that about two-thirds of pulmonary lesions found in association with extrapulmonary involvement presented characteristic features of the haematogenous group. Pinner, from a study of autopsy material, found that small tubercles of different age in both the lung and extrapulmonary organs were a characteristic feature of nonmiliary haematogenous tuberculosis. This he interpreted as meaning that several seedings had taken place at different times.

I am reporting this group of cases because it may help to answer some of the contentions that have been brought out to explain the high death rate from tuberculosis among Mexicans in this country. The explanation generally centres around the poor living conditions, lack of nourishing food and inability to obtain good medical care and hospitalization among the Mexicans in the United States.

In this study a group of 53 Mexican laborers is compared with a group of 209 white laborers. The patients were all male adults. They were all employed by the Southern Pacific Railroad at the time the tuberculosis was diagnosed. While the standard of living of the Mexicans was undoubtedly lower than that of the white employees, they were receiving sufficient remuneration to provide adequate food and shelter. All of the patients were examined before they were employed and presumably did not have tuberculosis at that time. They were all provided with free medical attention during their employment. It was my observation that the Mexicans were as prone to avail themselves of the free medical attention as were the white employees. After tuberculosis was detected all of the employees were given the same hospitalization under exactly the same conditions for a period of one year.

A comparison of the two groups brought out a number of interesting points. In reviewing the histories it seemed that the Mexicans were more prone to be acutely ill at the onset of tuberculosis. The average duration of the symptoms before admission was less than six months in the Mexican group and slightly over eight months in the white group.

A study of the roentgenograms on admission showed that 35 (66 per cent) of the 53 Mexican patients had what appeared to be haematogenous or exudative types of tuberculosis while only 13 (25 per cent) had predominantly productive or fibroid lesions. In four cases the exact nature of the underlying lesion was not determined because of pleurisy with effusion. In the group of white patients only 17 (8 per cent) were haematogenous or exudative while 187 (89 per cent) were predominantly

productive or fibroid lesions. In five cases the lesions were atypical or not classified. In 41 (79 per cent) of the Mexican patients the lesions were bilateral as opposed to 142 (68 per cent) of bilateral lesions in white patients. Cavities were present in 22 (41 per cent) of the Mexicans and 131 (63 per cent) of the whites.

In all of the Mexican patients reported here a positive diagnosis of tuberculosis was made by laboratory methods at some time during their hospitalization. However, in only 41 were tubercle bacilli found on direct smear at the time of admission. In 26 (50 per cent) of the Mexican patients the sputum remained positive while only 45 (21 per cent) of the white patients had a persistently positive sputum during their hospitalization. In some of the Mexican patients it was difficult to obtain a positive sputum. In several the sputum was negative on direct smear, but guinea pigs injected with sputum developed tuberculosis. This is in accordance with the findings of Pinner and Reisner

TABLE 1

*Results of treatment of Mexicans compared with whites*

| | NUMBER OF CASES | ARRESTED OR CURED | APPARENTLY ARRESTED | IMPROVED | UNIMPROVED | DIED IN SANATORIUM | DIED WITHIN 5 YEARS |
|---|---|---|---|---|---|---|---|
| Mexicans | 53 | 4 (7.5%) | 1 (1.9%) | 19(35%) | 4(7.5%) | 17(32%) | 25(47%) |
| Whites | 209 | 32(15.3%) | 33(15.8%) | 94(45%) | 9(4.3%) | 23(11%) | 44(21%) |

who report that in chronic haematogenous tuberculosis the tubercle bacilli are often difficult to demonstrate in the sputum.

The progress of the Mexicans during their hospitalization was not encouraging. Among the Mexicans 49 per cent developed tuberculosis elsewhere in the body, whereas only 20 per cent of the white patients had extrapulmonary lesions. The extrapulmonary lesions in the Mexicans were distributed as follows: pleurisy with effusion 11, tuberculous enteritis 6, tuberculous laryngitis 5, tuberculous epididymitis 4, tuberculous meningitis 1, tuberculous peritonitis 1, tuberculosis of the knee 1, tuberculous osteomyelitis of the skull 1, tuberculosis of the spine 1, and tuberculous rectal fistula 1.

Collapse therapy was used in 71 per cent of the Mexicans as compared with 75 per cent of the whites. Of the 38 Mexicans in which collapse therapy was used, pneumothorax was used alone in 12 cases, phrenic interruption alone in 12 cases and phrenic interruption combined with pneumothorax in 13 cases. There were 5 cases in which an acute miliary

spread, and 7 cases in which haematogenous or bronchogenic spread occurred during the course of the pneumothorax. There was only one patient in which the lesion indicated and the condition warranted a thoracoplasty.

The end results in the group of Mexicans were much less satisfactory than in the group of whites (see table 1). Of the Mexicans 32 per cent died in the sanatorium compared with only 11 per cent of the whites. Also 47 per cent of the Mexicans were dead within 5 years compared with 21 per cent of the whites in a similar period. Only 7.5 per cent of the Mexicans could be considered arrested or cured while 15.3 per cent of the whites were so classified.

## SUMMARY

A group of tuberculous, adult, male, Mexican laborers is compared with a similar group of tuberculous, adult, male, white laborers; all were employees of the Southern Pacific Railroad. They all had similar occupations and all had the same advantages regarding medical attention and hospitalization. The Mexicans were more prone to have haematogenous types of tuberculosis with a tendency toward the development of extrapulmonary lesions. Collapse therapy was less effective in the Mexicans and in some cases proved to be dangerous. The end results showed fewer cures and a much higher mortality rate among the Mexicans.

## BIBLIOGRAPHY

(1) Alarcón, D. G.: Racial aspect of tuberculosis in Mexico, Trans. Natl. Tuberc. Assn., 1936, p. 216.
(2) Grethmann, W.: Protracted hematogenous multiform tuberculosis, Ibid., 1936, p. 80.
(3) Miller, J. A.: Haematogenous pulmonary tuberculosis, Amer. Rev. Tuberc., 1934, *29*, 489.
(4) Rodriguez Pastor, J.: Tuberculosis in Puerto Rico, Trans. Natl. Tuberc. Assn., 1936, p. 218.
(5) Pinner, M.: Discussion on tuberculosis among different peoples, Ibid., 1936, p. 223.
(6) Pinner, M.: Hematogenous (non-miliary) pulmonary tuberculosis, Amer. Jour. Roent., 1934, *31*, 442.
(7) Reisner, D.: Hematogenous tuberculosis of lungs, Med. Clin. North America, 1936, *20*, 759.

# A TUBERCULOSIS SURVEY IN JAMAICA[1]

E. W. FLAHIFF

## PURPOSE OF STUDY

This paper covers a study of the epidemiology of tuberculosis in rural Jamaica, British West Indies, and is a condensed form of a more detailed report which is being published by the Government of Jamaica.

In 1931 Wells and Smith (1) started surveys in Kingston, the capital of the island. Four separate districts, representing various economic classes of the population, were selected for these studies. The surveys in rural Jamaica were begun in March, 1932 and were completed by the end of May, 1934. The object was to secure information concerning tuberculosis in large and small towns and rural areas throughout the island comparable to that which had been obtained in Kingston.

Since the greater part of the population of Jamaica outside of Kingston and Lower St. Andrew is very poor, the areas for study in the towns were selected to represent the poorest classes. In the selection of areas in the rural parts of the island outside of towns, the economic status of the population was not a factor, since practically all the peasants are of the poorest class. Since it was desirable to study tuberculosis in typical rural sections, eliminating in so far as possible contact of the population with that of town and city, rural survey areas were selected in sparsely settled districts situated as far distant as possible from main traffic lines and towns.

## DESCRIPTION OF JAMAICA

The extreme length of Jamaica is 144 miles; its greatest width is 49 miles. As shown on the accompanying map, the island is divided into fourteen parishes. It has a few small towns and many settlements of about a hundred persons each. The rest of the population is scattered throughout the rural areas. There are only three towns in addition to Kingston that are of any size, namely, Montego Bay in St. James, Port

[1] The studies and observations on which this paper is based were conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation and the Government of Jamaica.

Antonio in Portland, and Spanish Town in St. Catherine, and none of these exceeds 15,000 in population.

The last official census for Jamaica was taken in 1921. The population then was found to number 858,118, of which 456,145, or 53.2 per cent, were females, and 401,973, or 46.8 per cent, males. The estimated population on June 30, 1935, was 1,081,854. According to the 1921

THE ISLAND OF JAMAICA, B. W. I.

SURVEY AREAS

1. Montego Bay
2. Rural St. James
3. Spanish Town
4. Rural St. Catherine
5. Kingston
6. Port Antonio
7. Rural Portland
8. Hope Bay
9. Manchioneal

census, the percentage distribution of the population for the island, by race and color, was:

| | *per cent* |
|---|---|
| Black | 77.0 |
| Colored | 18.3 |
| East Indian | 2.2 |
| White | 1.7 |
| Chinese | 0.4 |
| Not noted | 0.4 |

The density of the population was 193 persons per square mile, with an average of 4.4 persons per inhabited dwelling. There are 692 elementary

schools in the island with an attendance of about 125,000 children. About 53 per cent of the entire population are able to read and write.

Jamaica is almost entirely an agricultural country. The largest part of its working population is composed of agricultural laborers or small farmers. There are about 100,000 peasant proprietors on the island. More than half the population over 15 years of age is engaged in tilling the soil or doing work connected with agriculture. The other adult inhabitants are largely merchants, shopkeepers, domestic servants and teachers.

## DESCRIPTION OF THE SURVEY AREAS

The survey areas selected were as follows: (*a*) a large town (Montego Bay) and a rural area in the parish of St. James, to represent the western end of the island; (*b*) a large town (Port Antonio) and a rural area in the parish of Portland, to represent the eastern end of the island; (*c*) a large town (Spanish Town) and a rural area in the parish of St. Catherine, to represent the central portion of the island fairly close to Kingston; (*d*) two small towns at some distance from Kingston, one on the north shore (Hope Bay) and one on the eastern shore (Manchioneal), to represent conditions in small towns of the island. The location of these areas is shown on the map on page 561.

St. James is one of the smaller parishes, with an estimated population in June, 1933 of 50,946. Its chief town, Montego Bay, ranks next to Kingston in point of commercial importance and is the third largest town on the island. Its population is estimated as 7,896.

The parish of Portland had, in 1933, an estimated population of 58,366. Port Antonio, its most important town (fourth largest on the island), is the centre of most of the shipping business for the parish, and has an estimated population of 7,526.

The parish of St. Catherine had, in 1933, an estimated population of 114,289. The largest town in the parish is Spanish Town, the ancient capital of the island, which has an estimated population of 10,433.

Hope Bay is a small town with a population of 881, situated on the north shore of the island in the parish of Portland. It is a minor shipping point and a market centre for the inhabitants of the district. In these respects it is typical of all other small coastal towns on the island. Manchioneal is a small town on the east shore of Jamaica in the parish of Portland with a population of 1,193, and is similar to Hope Bay. The small inland towns are well represented by these two communities, being, like them, market centres for the inhabitants of the surrounding districts.

## METHOD OF SURVEY

The field staff conducting the studies here reported consisted of the medical officer in charge of the survey, one nurse, and one secretary who also acted as laboratory technician.

The first step in each area was to take a house-to-house census until a sample of approximately 1,000 residents had been visited in the rural areas, the whole population of the small towns, and a number of blocks in the large towns.

The medical director and the nurse then went from house to house giving the tuberculin tests. This enabled them to meet all the individuals in the survey areas, obtain their confidence, and answer any questions.

The tuberculin test was given intracutaneously, and fresh dilutions were made daily for these tests. The initial test was with 0.01 mgm. of Old Tuberculin, given on the anterior surface of the upper left forearm. It was examined after 48 hours and, if negative, a second test, using 1.0 mgm., was given on the anterior surface of the upper right forearm. Some investigators have used an intermediate test of 0.1 mgm., but in this work no reactions to 1.0 mgm. were severe enough to make an intermediate test necessary. The positive reactions were divided into four groups (one plus to four plus) (2):

A reaction expressed by one plus (+) is a definite oedema, not more than 10 mm. in diameter and raised about 1 mm.; the area of redness is less significant and is usually much larger.

A reaction of two plus (++) is a well defined oedema in an area from 10 to 15 mm. across and raised somewhat more than 1 mm.; with redness extending beyond the oedema.

A reaction of three plus (+++) is an extensive oedema measuring more than 15 mm. across but with no necrosis of the skin; and in a few instances redness extending along the course of the lymphatics adjacent to the site of injection.

A reaction of four plus (++++) is extensive oedema, redness, and a spot of necrosis; it may be associated with malaise and an elevation of temperature.

In these surveys only the persons who reacted to the tuberculin test were given X-ray examination of the chest. In the three large towns

each reactor was notified to report to the central office for an X-ray examination. As soon as the responses to this invitation began to fall off, a station wagon was secured from Kingston, and the reactors who had not presented themselves for examination were called for at their homes. This procedure served to increase greatly the percentage of reactors X-rayed. In the small towns and rural areas the reactors were notified to meet at certain points on one or two days of each week and motor buses brought them to the large towns for X-ray examinations.

The X-ray unit was a Kelley-Koett portable X-ray machine, type L.D., serial 324, 115 volt, 40 cycles. A 30 M.A. Coolidge tube was used. The routine X-ray examination consisted in taking a single anteroposterior film. When these were read, suspicious cases, or those with incomplete diagnosis, were brought for further X-ray examination, and both anteroposterior and rotation films were taken. On every person who showed a lesion of any description a thorough physical examination and a sputum examination were done and a detailed history was obtained.

## DISTRIBUTION OF POPULATION BY AGE AND SEX IN THE LARGE TOWNS, SMALL TOWNS, RURAL AREAS, AND JAMAICA AS A WHOLE

In table 1 is shown the distribution of the population by age and sex in the three large towns, two small towns and three rural areas. In addition, the table shows the percentage of the total population by sex, in each age group, with a similar percentage distribution of the population for the whole island as given in the 1921 census. In the large towns 63.5 per cent of the total population were females, and 28.7 per cent of the total population were under 15 years of age. In the small towns 54.3 per cent were females, with 33.1 per cent of the total population under 15 years of age. In rural areas 51.0 per cent were females and 36.5 per cent of the total population were under 15 years of age.

If the distribution for the island as a whole is accepted as the normal, it is found that from infancy to about 20 years of age there is considerable variation in the percentage distribution of the population in the three survey divisions, with a higher than normal percentage of children in the rural areas and less than normal in the large and small towns. From about 40 years of age upward, the percentages of the population in each age group of each area closely approximate each other and the distribution of the population of the island as a whole. There is a slightly

TABLE 1

*Distribution of population by age and sex in large towns, small towns, rural areas, and the Island of Jamaica*

| SURVEY AREAS | 0–4 YEARS | | 5–9 YEARS | | 10–14 YEARS | | 15–19 YEARS | | 20–29 YEARS | | 30–39 YEARS | | 40–49 YEARS | | 50–59 YEARS | | 60+ YEARS | | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | |
| Large towns | | | | | | | | | | | | | | | | | | | |
| Population | 89 | 133 | 96 | 128 | 84 | 102 | 61 | 124 | 174 | 419 | 134 | 223 | 82 | 112 | 54 | 71 | 28 | 85 | 2,199 |
| Per cent of total population | 4.0 | 6.0 | 4.4 | 5.8 | 3.8 | 4.6 | 2.8 | 5.6 | 7.9 | 19.1 | 6.1 | 10.1 | 3.7 | 5.1 | 2.5 | 3.2 | 1.3 | 3.9 | 99.9 |
| Small towns | | | | | | | | | | | | | | | | | | | |
| Population | 102 | 94 | 105 | 123 | 68 | 83 | 68 | 91 | 149 | 206 | 108 | 114 | 68 | 90 | 62 | 63 | 62 | 79 | 1,735 |
| Per cent of total population | 5.9 | 5.4 | 6.0 | 7.1 | 3.9 | 4.8 | 3.9 | 5.2 | 8.6 | 11.9 | 6.2 | 6.6 | 3.9 | 5.2 | 3.6 | 3.6 | 3.6 | 4.5 | 99.9 |
| Rural areas | | | | | | | | | | | | | | | | | | | |
| Population | 164 | 137 | 240 | 221 | 189 | 149 | 129 | 159 | 277 | 308 | 184 | 204 | 123 | 171 | 105 | 107 | 65 | 81 | 3,013 |
| Per cent of total population | 5.4 | 4.5 | 8.0 | 7.3 | 6.3 | 4.9 | 4.3 | 5.3 | 9.2 | 10.2 | 6.1 | 6.8 | 4.1 | 5.7 | 3.5 | 3.5 | 2.2 | 2.7 | 100.0 |
| Island of Jamaica 1921 census—per cent of total population | 6.5 | 6.5 | 7.0 | 7.0 | 6.1 | 6.1 | 4.8 | 5.4 | 7.5 | 10.1 | 4.9 | 6.4 | 4.6 | 5.0 | 2.6 | 3.0 | 2.6 | 3.5 | 99.6 |

Total population for Island of Jamaica according to 1921 census: 858,118—Males: 401,973, or 46.8 per cent; Females: 456,145, or 53.2 per cent.

greater percentage of females in each instance. However, from 20 to 39 years of age there is a wide variation, reaching a peak in the 20 to 29 group. The females in the large towns are much more numerous, with a corresponding drop in the percentage of males. In the small towns a similar situation exists, but to a lesser degree. In the rural areas the reverse is true, with about normal percentage of females and a higher than normal percentage of males.

The explanation lies in the occupation of the people. The females tend to migrate toward the larger centres to serve as domestic servants, sew, or work as laborers in loading fruit, breaking stone for road construction, and other occupations. The males remain in greater numbers in the rural areas in cultivation work. The households are more stable in

TABLE 2

*The distribution of the population in the three survey divisions, according to color*

| COLOR | LARGE TOWNS | | SMALL TOWNS | | RURAL AREAS | |
|---|---|---|---|---|---|---|
| | Total number | Per cent of total population | Total number | Per cent of total population | Total number | Per cent of total population |
| Black | 1,870 | 85.0 | 1,577 | 90.9 | 2,750 | 91.3 |
| Dark brown | 245 | 11.1 | 70 | 4.0 | 150 | 5.0 |
| Light brown | 66 | 3.0 | 48 | 2.8 | 92 | 3.0 |
| Others | 18 | 0.8 | 40 | 2.3 | 21 | 0.7 |
| Total | 2,199 | 99.9 | 1,735 | 100.0 | 3,013 | 100.0 |

rural areas, as shown by the increased percentage of children in the rural areas over the percentage found in the larger towns and small towns.

*The occupations of the inhabitants of large and small towns:* As previously described, the occupation followed in rural areas is entirely associated with agriculture. In the large and small towns, adults are chiefly domestic servants, laborers, housewives and dressmakers. All of these, except laborers, are almost entirely females, and even among the laborers more than half are females. This illustrates why the young females tend to migrate to the towns, leaving the males to do most of the cultivation in rural areas.

*Color:* The distribution of the population in the three survey divisions according to color is shown in table 2. The general distribution does not agree with that of the island as a whole, but shows a greater percentage of blacks in small towns and rural areas than in the large towns. Since the majority of lighter complexioned natives and members of other

nationalities reside in Kingston, it is believed that the table is a fairly accurate representation of the distribution outside the capital.

## RESULTS OF TUBERCULIN TESTS

The important epidemiological features of the combined three large towns, the two small towns and the three rural areas will be presented. In the large towns, the total population of the survey districts was 2,199, of which 1,480 (67.3 per cent) received complete tuberculin tests. In the small towns, the total population was 1,735, of which 1,453 (83.7 per cent) received complete tuberculin tests. In the rural areas, the total population was 3,013, of which 2,480 (82.3 per cent) received complete tuberculin tests. In all districts better coöperation was obtained from the women, particularly in the large towns, because more women were found in their homes when visits were made.

In table 3 is shown the percentage of persons who reacted to tuberculin, by age and sex. In the totals for both sexes, it may be seen that the percentage of female reactors for all areas is slightly higher than that for males. In none of the areas is there any significant difference between the sexes. The average percentage of tuberculin reactors for children and adults in these divisions is shown at the bottom of this table. (Throughout this paper, reference to "children" pertains to all individuals under 15 years of age; persons over 15 years of age are classed as adults.) A significant feature of this table is the drop in the percentage of reactors in the age group 60+ in the large and small towns but not in the rural areas.

Dr. Hugo Muench (3) has kindly fitted catalytic curves to these three groups, and the following is quoted from his remarks on the results.

If the data are fitted only to the fiftieth year, the per cent positive in each case appears to approach a hundred. This would mean that the reversion rate is negligible. The annual rate of increase of positives on this basis for the three divisions is:

| | *per cent* |
|---|---|
| Large towns | 7.97 |
| Small towns | 4.82 |
| Rural areas | 3.36 |

The curves based on this rate fit the data very well up to fifty years, but after this they do not. Even the three rural areas, while they show no actual decrease of positives over fifty years of age, do after this time fall off considerably from the rate they have been following.

TABLE 3

*The percentage of the population with completed tuberculin tests showing positive reaction, by age and sex*

| AGE | SEX | LARGE TOWNS | | SMALL TOWNS | | RURAL AREAS | |
|---|---|---|---|---|---|---|---|
| | | Number with complete tuberculin tests | Per cent positive | Number with complete tuberculin tests | Per cent positive | Number with complete tuberculin tests | Per cent positive |
| *years* | | | | | | | |
| 0–4 | M | 56 | 19.6 | 85 | 18.8 | 143 | 9.1 |
| | F | 100 | 21.0 | 75 | 20.0 | 113 | 8.0 |
| 5–9 | M | 82 | 40.2 | 94 | 16.0 | 211 | 21.3 |
| | F | 112 | 38.4 | 110 | 21.8 | 193 | 10.4 |
| 10–14 | M | 73 | 61.6 | 60 | 38.3 | 164 | 27.4 |
| | F | 88 | 59.1 | 71 | 29.6 | 137 | 30.7 |
| 15–19 | M | 31 | 67.7 | 50 | 64.0 | 100 | 41.0 |
| | F | 97 | 74.2 | 85 | 62.4 | 140 | 45.7 |
| 20–29 | M | 75 | 94.7 | 103 | 71.8 | 199 | 66.8 |
| | F | 308 | 87.0 | 177 | 74.6 | 252 | 57.5 |
| 30–39 | M | 53 | 100.0 | 78 | 88.5 | 140 | 72.1 |
| | F | 171 | 91.2 | 106 | 75.5 | 184 | 71.7 |
| 40–49 | M | 39 | 97.4 | 47 | 83.0 | 84 | 76.2 |
| | F | 79 | 94.9 | 82 | 89.0 | 138 | 73.2 |
| 50–59 | M | 17 | 100.0 | 42 | 83.3 | 75 | 72.0 |
| | F | 51 | 90.2 | 61 | 85.2 | 94 | 76.6 |
| 60+ | M | 10 | 60.0 | 52 | 69.2 | 48 | 79.2 |
| | F | 38 | 89.5 | 75 | 74.7 | 65 | 73.8 |
| Total | M | 436 | 67.7 | 611 | 55.5 | 1,164 | 45.9 |
| | F | 1,044 | 73.5 | 842 | 60.1 | 1,316 | 48.1 |
| Total | | 1,480 | 71.8 | 1,453 | 58.1 | 2,480 | 47.1 |

Percentage tuberculin-positive persons under 15 years of age:

| | |
|---|---|
| Large towns | 40.1 |
| Small towns | 23.0 |
| Rural areas | 18.1 |

Percentage tuberculin-positive persons over 15 years of age:

| | |
|---|---|
| Large towns | 88.4 |
| Small towns | 76.3 |
| Rural areas | 65.4 |

When the period 50–70 years is included the rates are changed somewhat as follows:[2]

| | | per cent |
|---|---|---|
| Large towns | A | 9.42 |
| | B | 0.92 |
| Small towns | A | 5.92 |
| | B | 1.20 |
| Rural areas | A | 3.77 |
| | B | 0.73 |

The relative difference between areas is much the same, but the curves become distorted in trying to account for the reversion rate exhibited in the last two decades. It looks almost as though there was a perfectly steady rate of increase in all areas for the first 40 or 50 years, and that considerable reversion occurred after this time.

Table 4 shows the percentage of tuberculin reactors in each age group according to color.

Black, dark brown and light brown represent the Negro population and various Negro-white mixtures and no other races. "Others" is a small group made up of East Indians, Chinese and a few Armenians. There is no appreciable difference in the trend of the curve in black, dark brown and light brown, showing that the tuberculin reaction among persons of racial mixture does not differ in frequency from that of those wholly Negro. In the group entitled "others" there are not sufficient numbers to draw definite conclusions.

Table 5 presents the percentage distribution of the severity of the tuberculin reaction in each of the survey divisions.

It will be seen that in the large towns the majority of the reactors in all age groups were sensitive to 0.01 mgm.; and approximately one-half of all reactions to 0.01 mgm. were two, three or four plus.

In the small towns the majority of reactors in all age groups were sensitive to 0.01 mgm., but there was a larger percentage who reacted only to 1.0 mgm. than was found in the large towns. Similar to the large towns, approximately one-half of the persons who reacted to 0.01 mgm. had two, three or four plus reactions.

In the rural areas the picture is considerably changed. The percentage of reactors who were sensitive only to 1.0 mgm. was comparable to that found in the small towns, but among the persons who reacted to 0.01 mgm. there was a lower percentage who showed one plus reactions than was found in either large or small towns.

[2] A equals the annual rate of increase of positive reactions; B equals the annual rate of decrease of positive reactions.

The following is offered as an explanation of these observations:

(*1*) In large towns the increased density of population is more conducive to casual infection and hence the individuals in these areas are

TABLE 4

*The percentage of tuberculin reactors in each age group according to color*
(All areas)

| AGE | COLOR | | | | | | |
|---|---|---|---|---|---|---|---|
| | Black | | Dark brown | | Light brown | | Others |
| | Number tested | Per cent reactors | Number tested | Per cent reactors | Number tested | Per cent reactors | Number tested |
| *years* | | | | | | | |
| 0–4 | 504 | 15.5 | 46 | 6.5 | 14 | 21.4 | 8 |
| 5–9 | 715 | 22.7 | 56 | 23.2 | 24 | 16.7 | 7 |
| 10–14 | 540 | 37.8 | 41 | 43.9 | 10 | 60.0 | 2 |
| 15–19 | 450 | 56.4 | 34 | 52.9 | 15 | 60.0 | 4 |
| 20–29 | 996 | 73.3 | 72 | 77.8 | 28 | 71.4 | 18 |
| 30–39 | 652 | 80.5 | 60 | 81.7 | 15 | 80.0 | 5 |
| 40–49 | 426 | 82.6 | 23 | 82.6 | 16 | 93.8 | 4 |
| 50–59 | 302 | 80.5 | 22 | 90.9 | 12 | 83.3 | 4 |
| 60+ | 254 | 75.2 | 21 | 76.2 | 10 | 80.0 | 3 |
| Total..... | 4,839 | 56.6 | 375 | 56.5 | 144 | 60.4 | 55 |

TABLE 5

*The percentage of frequency of reactors to tuberculin according to intensity of reaction, by age*

| AGE | LARGE TOWNS | | | SMALL TOWNS | | | RURAL AREAS | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.01 mgm. | | Positive to 1.0 mgm. | 0.01 mgm. | | Positive to 1.0 mgm. | 0.01 mgm. | | Positive to 1.0 mgm. |
| | 2, 3 and 4 plus | 1 plus | | 2, 3 and 4 plus | 1 plus | | 2, 3 and 4 plus | 1 plus | |
| *years* | | | | | | | | | |
| 0–4 | 7.1 | 5.1 | 8.3 | 4.4 | 11.9 | 3.1 | 4.7 | 0.4 | 3.5 |
| 5–9 | 14.4 | 12.4 | 12.4 | 5.9 | 5.9 | 7.4 | 5.4 | 3.5 | 7.2 |
| 10–14 | 21.7 | 21.7 | 16.8 | 9.2 | 10.7 | 13.7 | 12.0 | 5.6 | 11.3 |
| 15–19 | 26.6 | 32.0 | 14.1 | 20.7 | 22.2 | 20.0 | 17.5 | 10.8 | 15.4 |
| 20–29 | 38.1 | 41.0 | 9.4 | 28.2 | 23.6 | 21.8 | 30.6 | 12.0 | 19.1 |
| 30–39 | 41.1 | 42.9 | 9.4 | 34.2 | 28.3 | 18.5 | 36.7 | 14.2 | 21.0 |
| 40–49 | 44.9 | 36.4 | 14.4 | 33.3 | 27.1 | 26.4 | 37.4 | 16.2 | 20.7 |
| 50–59 | 41.2 | 47.1 | 4.4 | 31.1 | 30.1 | 23.3 | 46.2 | 12.4 | 16.0 |
| 60+ | 27.1 | 43.7 | 12.5 | 17.3 | 27.6 | 27.6 | 41.6 | 19.5 | 15.0 |
| Total..... | 29.7 | 30.9 | 11.1 | 20.5 | 20.2 | 17.4 | 23.3 | 9.6 | 14.2 |

much more liable to develop a positive tuberculin reaction. Since these casual infections may be frequently repeated, it is possible that the reinfection produces a greater degree of sensitiveness (percentage of persons

who react to 0.01 mgm.) but with a tendency to maintain a balance between host and parasite at a stage of less severity (more reactors one plus to 0.01 mgm.).

(*2*) In small towns the condition is somewhat the same except that with the decrease in density of population there is a decrease in the opportunity for casual infections, and a corresponding fall in the number of reactors. Similarly, the decreased opportunity for reinfection would explain the greater percentage who react only to 1.0 mgm. (healing stage of more severe infection).

(*3*) In rural areas the smaller number of reactors would be explained by the lessened opportunity for infection. The increased severity of the reactions to 0.01 mgm. may be due to the relatively infrequent chance of reinfection. The persons who react weakly may be in the healing stage of a first infection, and many adults who are tuberculin negative may have completely healed first infections. Then, when and if reinfection does occur, it may resemble a first infection and produce a more intense reaction, the even balance between host and parasite not being maintained. This would result in a wider band of reactors to 1.0 mgm. throughout life and more frequent intensive reactions late in life, and a lower level of infection in the population at large throughout life.

## RESULTS OF X-RAY EXAMINATIONS

The classification of tuberculosis as given throughout this paper is that used at the Henry Phipps Institute in Philadelphia, as described by Opie (4):

I. *Manifest Pulmonary Tuberculosis*

(1) Manifest pulmonary tuberculosis with sputum negative for tubercle bacilli:
   (a) Adult type
   (b) Childhood type

(2) Manifest pulmonary tuberculosis with tubercle bacilli in sputum:
   (a) Adult type
   (b) Childhood type

   A type called "undetermined" has been added for both sputum-positive and sputum-negative cases where doubt exists as to the proper classification.

II. *Latent Tuberculosis*
(1) Latent apical tuberculosis

(2) Latent infiltration (childhood type):
(a) Soft or flocculent
(b) Strandlike

(3) Calcified pulmonary nodule

(4) Tuberculosis of tracheobronchial lymph nodes:
(a) Calcified
(b) Massive caseous

In this survey, as mentioned previously, no attempt was made to X-ray persons who did not react to 0.01 or 1.0 mgm. of tuberculin. In following this procedure, undoubtedly a few calcified nodules of lungs or lymph nodes were missed. With manifest tuberculosis the reaction is rarely absent save in the terminal stages of the disease.

In the large towns 1,062 persons reacted to tuberculin, and 884 (83.2 per cent) received X-ray examination of the chest. In the small towns 845 individuals reacted, and 582 (68.9 per cent) were X-rayed. In the rural areas 1,167 individuals reacted, and 1,029 (88.2 per cent) were X-rayed.

About the same coöperation was obtained from both sexes in all areas. In the small towns the percentage of reactors X-rayed was considerably smaller because they were not willing to complete the examinations.

When the reactors to tuberculin are considered alone, it is found that the adults had a very constant percentage of lesions (all lesions combined, as revealed by X-ray examination) in the three survey divisions, varying from 7.7 to 8.2 per cent. Among reacting children, the percentage of lesions shown by X-ray examination was more variable (4.5 per cent to 11.5 per cent) and higher in the large and small towns.

In table 6 is shown the frequency of various tuberculous lesions in the three survey divisions. To determine the population base for this table, the number of individuals with completed tuberculin tests was multiplied by the percentage of reactors actually given X-ray examinations, and this number was used in computing the indices of lesion frequency. This procedure is based on the assumption that the nonreactors had no lesions. As stated previously, a small number of calcified lesions were probably missed.

The total frequency of lesions was greatest in the large towns, next in small towns, and least in rural areas. The distribution of children

TABLE 6

*The percentage of frequency of various tuberculous lesions revealed by X-ray examination, by age**

| AGE | LARGE TOWNS | | | | | SMALL TOWNS | | | | | RURAL AREAS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Manifest tuberculosis | Latent lesions | | | Total lesions | Manifest tuberculosis | Latent lesions | | | Total lesions | Manifest tuberculosis | Latent lesions | | | Total lesions |
| | | Infiltration childhood type | Calcified lesions | Apical lesions | | | Infiltration childhood type | Calcified lesions | Apical lesions | | | Infiltration childhood type | Calcified lesions | Apical lesions | |
| *years* | | | | | | | | | | | | | | | |
| 0–4 | 2.4 | — | — | — | 2.4 | 1.3 | — | — | — | 1.3 | — | — | — | — | — |
| 5–14 | 0.64 | — | 4.5 | — | 5.1 | — | 0.37 | 0.74 | — | 1.1 | — | — | 1.3 | 0.33 | 1.6 |
| 15+ | 1.5 | 0.13 | 3.5 | 1.6 | 6.8 | 2.0 | — | 3.2 | 1.1 | 6.3 | 0.07 | — | 3.6 | 1.3 | 5.1 |
| Total.... | 1.4 | 0.08 | 3.4 | 1.1 | 5.9 | 1.4 | 0.10 | 2.3 | 0.70 | 4.5 | 0.05 | — | 2.6 | 0.91 | 3.6 |

* Adjusted to total population given tuberculin tests.

TABLE 7

*The percentage of frequency of various tuberculous lesions revealed by X-ray examination, by sex and age**

| AGE | SEX | LARGE TOWNS | | | | SMALL TOWNS | | | | RURAL AREAS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Manifest tuberculosis | Latent lesions | | Total lesions | Manifest tuberculosis | Latent lesions | | Total lesions | Manifest tuberculosis | Latent lesions | | Total lesions |
| | | | Calcified lesions | Apical lesions | | | Calcified lesions | Apical lesions | | | Calcified lesions | Apical lesions | |
| *years* | | | | | | | | | | | | | |
| 20–29 | M | 1.6 | — | — | 1.6 | — | — | — | — | — | 0.55 | — | 0.55 |
| | F | 2.5 | 4.6 | 1.7 | 8.8 | 2.5 | 3.3 | 0.82 | 6.6 | — | 6.8 | 2.3 | 9.1 |
| 30–59 | M | 2.2 | 5.6 | — | 7.8 | 2.9 | 3.8 | 1.9 | 8.7 | 0.37 | 2.6 | 0.37 | 3.4 |
| | F | 1.2 | 3.2 | 3.2 | 7.5 | 1.7 | 3.5 | 1.7 | 7.0 | — | 4.8 | 2.7 | 7.5 |
| 20–59 | M | 2.0 | 3.3 | — | 5.3 | 1.7 | 2.2 | 1.1 | 5.0 | 0.22 | 1.8 | 0.22 | 2.2 |
| | F | 1.8 | 3.9 | 2.4 | 8.2 | 2.0 | 3.4 | 1.4 | 6.8 | — | 5.4 | 2.6 | 7.9 |

* Adjusted to total population given tuberculin tests.

with lesions differs significantly from that of adults in the three survey divisions owing to the larger proportion of children with lesions in the large towns ($\chi^2 = 7.333$; $P = .026$). There were 32 persons with

manifest tuberculosis found during the survey, giving indices of 1.4 per cent in both large and small towns, and .05 per cent in the rural areas. The frequency of latent lesions in adults is similar in all areas. It is suggested that in rural areas the inhabitants have as much chance of becoming infected sometime in their lives as persons in the large and small towns but, owing to lessened chance of repeated infections, or to living conditions (better nutrition, active life in the open, etc.) that favor the healing of lesions, the disease does not develop but resolves itself into a latent lesion.

To show sex differences in the infection index, table 7 is offered. This table compares the adults in the age groups of 20 to 29 and 30 to 59 years.

The peak of the infection level among females occurs in the age group of 20 to 29 years, and the frequency of lesions revealed by X-ray examination is highest among females in this age group, in each of the three survey divisions. The frequency of the various types of lesions in the age group of 20 to 29 is considerably higher in females than in males. In the age group of 30 to 59 years the frequency of lesions is greater among males in the towns, but in the rural areas lesions among the females are more numerous.

No attempt is made here to present the frequency of various tuberculous lesions by color, since our total numbers in all groups except black are too small to be significant.

## THE RELATIONSHIP OF THE SEVERITY OF THE TUBERCULIN REACTION TO THE AMOUNT OF TUBERCULOUS DISEASE

Table 8 shows the frequency of all tuberculous lesions, with varying intensity of the tuberculin reaction, in all areas combined.

The trend of lesion frequency with the intensity of tuberculin reaction for all reactors given X-ray examination is significant ($\chi^2 = 12.82$; $P = .005$). That for children under 15 years is also significant ($\chi^2 = 13.17$; $P = .004$). The trend for persons over 15 is not significant ($\chi^2 = 5.736$; $P = .127$). It will be noted that no lesions were found by X-ray examination in the age group of 0 to 4 years in reactors to 1.0 mgm. of Old Tuberculin, but the percentage of lesions increases with the severity of the reaction to 0.01 mgm. Among children, aged 5 to 14 years, the percentage with lesions increases with the intensity of the reaction up to ++ to .01 mgm., with which there is an exceptionally

high percentage of lesions. There is a drop in the percentage of lesions with +++ and ++++ reactions. In the adult group there is also a rise in the percentage of lesions parallel with the severity of the reaction, but this is not so conspicuous as in children.

### TUBERCULOUS INFECTION IN HOUSEHOLDS WITH CASES OF LATENT TUBERCULOSIS, SPUTUM-NEGATIVE TUBERCULOSIS OR SPUTUM-POSITIVE TUBERCULOSIS (ALL AREAS)

Table 9 shows the frequency of tuberculous infection in persons in household contact with cases of latent tuberculosis, sputum-negative tuberculosis and sputum-positive tuberculosis.

The percentage reacting to tuberculin does not change unless the household contact is one of sputum-positive tuberculosis. The index

TABLE 8

*The frequency of tuberculous lesions according to the severity of the tuberculin reaction*

(All areas)

| AGE | REACTORS TO 1.0 MGM. | | 1 PLUS TO .01 MGM. | | 2 PLUS TO .01 MGM. | | 3 AND 4 PLUS TO .01 MGM. | |
|---|---|---|---|---|---|---|---|---|
| | Number X-rayed | Per cent lesions | Number X-rayed | Per cent lesions | Number X-rayed | Per cent lesions | Number X-rayed | Per cent lesions |
| *years* | | | | | | | | |
| 0–4 | 21 | — | 15 | 6.7 | 10 | 10.0 | 14 | 14.3 |
| 5–14 | 127 | 3.1 | 103 | 7.8 | 88 | 15.9 | 33 | 9.1 |
| 15+ | 493 | 5.7 | 684 | 7.6 | 667 | 8.8 | 240 | 10.0 |
| Total..... | 641 | 5.0 | 802 | 7.6 | 765 | 9.7 | 287 | 10.1 |

then jumps from 60 to 94 per cent. Lesion frequency among persons in contact with sputum-negative tuberculosis is 8.2 per cent, as compared with 2.1 per cent for those in households where there are persons with latent lesions only. The tuberculin reactions of sputum-positive and sputum-negative contacts are significantly different ($\chi^2 = 11.94$; $P = .000,5$), but the frequency of lesions is probably not.

*Foreign travel or residence in Kingston:* The number of individuals, in all areas, who gave a history of residence in Kingston is small. In the large towns 10.3 per cent of the population gave a history of foreign travel or residence in Kingston, while in the small towns 6.3 per cent gave such a history, and in the rural areas 3.0 per cent. Since the numbers giving this history are so small, no table of these data is included in this report. Consideration is limited to persons between 20 and 59 years

of age, since they are the ones most affected. In large towns, the tuberculin reaction in the group that has travelled is actually not so high as that for the remainder of the population. All other indices of infection are higher in the group that has travelled. None of the differences is significant.

*Household and sleeping room density:* No analysis of the frequency of infection or disease, on the basis of household or sleeping room density of the population, is offered. Since the best measure of the severity

TABLE 9

*The frequency of tuberculous infection among persons in accordance with the character of their contact with tuberculosis**

(All areas)

| AGE | TUBERCULIN REACTORS WITH NO X-RAY LESIONS | | | | | ONE OR MORE WITH LATENT TUBERCULOSIS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number tuberculin tested | Per cent reactors | Number of reactors X-rayed | Number with lesions | Per cent lesions† | Number tuberculin tested | Per cent reactors | Number of reactors X-rayed | Number with lesions | Per cent lesions† |
| *years* | | | | | | | | | | |
| 0–4 | 385 | 14.8 | 45 | — | — | 40 | 20.0 | 7 | — | — |
| 5–14 | 969 | 30.8 | 260 | — | — | 156 | 35.9 | 52 | 2 | 1.4 |
| 15+ | 2,411 | 79.6 | 1,674 | — | — | 299 | 77.9 | 202 | 7 | 2.7 |
| Total..... | 3,765 | 60.4 | 1,979 | — | — | 495 | 60.0 | 261 | 9 | 2.1 |
| | ONE OR MORE WITH SPUTUM-NEGATIVE TUBERCULOSIS | | | | | ONE OR MORE WITH SPUTUM-POSITIVE TUBERCULOSIS | | | | |
| 0–4 | 14 | 28.6 | 3 | — | — | 4 | 100.0 | 2 | 1‡ | 50.0 |
| 5–14 | 27 | 40.7 | 10 | 3 | 12.0 | 9 | 77.8 | 6 | 1 | 12.5 |
| 15+ | 60 | 78.3 | 39 | 4 | 8.0 | 19 | 100.0 | 18 | 1‡ | 5.6 |
| Total..... | 101 | 61.4 | 52 | 7 | 8.2 | 32 | 93.8 | 26 | 3 | 10.7 |

* All "key" cases have been excluded, consisting of 147 latent lesions, 20 sputum-negative lesions, and 10 sputum-positive lesions. By "key" cases are meant cases in each household from which the diagnosis for the household was made.

† Adjusted to total population given tuberculin tests.

‡ Cases of manifest sputum-negative tuberculosis.

of infection in the household, namely cases of manifest disease, is represented by so small a number in this survey, the results of such an analysis would be inconclusive and would add no important data. The mean size of the households and mean number of persons per sleeping room are given below:

| | *Large Towns* | *Small Towns* | *Rural Areas* |
|---|---|---|---|
| Persons per household..... | 6.055 ± .040 | 5.795 ± .038 | 5.684 ± .030 |
| Persons per sleeping room... | 3.075 ± .024 | 3.075 ± .022 | 3.810 ± .020 |

## SUMMARY AND CONCLUSIONS

1. In Jamaica the frequency of tuberculous infection as indicated by the tuberculin reaction is greatest in large towns, less in small towns, and least in rural areas.

2. The frequency of clinically manifest tuberculosis is about the same in both large and small towns, namely, 1.4 per cent of the population; and less in the rural areas, namely, .05 per cent of the population.

3. The percentage of latent lesions in the whole adult population of Jamaica is approximately the same in all survey areas regardless of density of population, and varies from about 3 to 6 per cent.

4. The frequency of tuberculous infection (as indicated by the tuberculin reaction) shows no difference between racial mixtures of Negro-white and of those wholly black.

5. There is no evident difference in the frequency of tuberculin reactions in the male and female sexes.

6. The frequency of clinically manifest tuberculosis reaches its peak, among the women, in the age group of 20 to 29 in the large and small towns. The frequency of all lesions revealed by X-ray examination is also highest among the women in this age group in all survey divisions.

7. There is a significant increase in frequency of all tuberculous lesions with the severity of the tuberculin reaction among children, but not among adults.

8. Of persons between the ages of 20 and 59 who are living in rural areas, small towns and large towns, approximately 7 per cent have lived in Kingston or elsewhere away from home. The recorded frequency of manifest tuberculosis and of tuberculous lesions is greater in those who have travelled than in those who have stayed at home, but the numbers are so small that the differences are not significant.

The author wishes to express his appreciation of the valuable assistance rendered by Dr. Persis Putnam in the analysis of the statistical data and for suggested interpretations.

## REFERENCES

(1) Wells, C. W., and Smith, H. H.: The epidemiology of tuberculosis in Kingston, Jamaica, Amer. Rev. Tuberc., 1936, *34*, 43.

(2) Hetherington, H. W., McPhedran, F. M., Landis, H. R. M., and Opie, E. L.: A survey to determine the prevalence of tuberculous infection in school children, Ibid., 1929, *20*, 421.

(3) Muench, H.: Derivation of rates from summation data by the catalytic curve, Jour. Amer. Stat. Assn., 1934, *29*, 25.

(4) Opie, E. L.: The epidemiology of tuberculosis in relation to the pathological anatomy and pathogenesis of the disease, reprinted from the Libman Anniversary Volumes, 1932, *3*, pp. 901–915.

# STUDIES IN AVIAN TUBERCULOSIS[1]

## 1. Avian Tubercle Bacilli in Generalized Disease in Swine

A. B. CRAWFORD

When the official program of the United States Bureau of Animal Industry for the eradication of bovine tuberculosis was started in 1917, it was assumed that tuberculosis in swine would decrease in direct ratio to the decrease in the disease in cattle, since it was believed that swine contracted tuberculosis almost exclusively from ingesting faeces of affected cattle or skim milk returned from creameries. However, the retention of swine for tuberculosis in federally inspected abattoirs continued for many years at practically the same level.

The avian type of tuberculosis in swine had been reported in sporadic instances prior to 1917, but the extensive rôle played by the avian tubercle bacillus in the retention of swine for tuberculosis was not definitely proved until Van Es and Martin (1) in 1925 reported the typing of avian tubercle bacilli from 185 of 209 swine showing lesions of tuberculosis. The avian type disease was still not recognized as more than a mild infection confined chiefly to the lymph nodes of the alimentary system.

In 1933, Stein (2) and Crawford (3) independently reported the recovery of avian tubercle bacilli from nodules in the spleen of swine.

Recently Feldman (4) reported the results of a study of 30 specimens of lesions from swine condemned for extensive tuberculosis in an abattoir in southeastern Minnesota in which 24 of the 30 cases were found by him to be due to the avian tubercle bacillus. As a result of this rather startling finding, arrangements were made through the officials of the Bureau of Animal Industry whereby this Station was furnished 36 specimens from swine condemned for generalized tuberculosis in government-inspected abattoirs in the States of South Dakota, Minnesota, Wisconsin, Ohio and Iowa. In these states, tuberculosis in poultry is known to be widespread and, with the exception of Iowa, the morbidity of tuberculosis in cattle was at that time less than 0.5 per cent.

[1] From the Animal Disease Station, Beltsville, Maryland, Bureau of Animal Industry, United States Department of Agriculture.

This work was of a preliminary nature in order to gain information for a broader survey and it is manifestly too small a number of specimens from such a wide territory on which to base an estimate of the comparative amounts of generalized avian and bovine tuberculous infection in swine in those states. Nevertheless, the fact that Feldman and the author found a majority of swine condemned for tuberculosis to be affected with the avian type of infection is significant that the avian tubercle bacillus is fast becoming of economic importance for other species of animals than poultry.

The tissue specimens received from the respective abattoirs consisted of a portion of or the whole spleen and a few lymph nodes, usually the bronchial or mediastinal. With but one or two exceptions, the spleen was used for inoculation purposes. The typing tests consisted of (*a*) animal inoculation, (*b*) testing the inoculated animals with avian and mammalian tuberculins, and (*c*) cultural differentiation.

The technique used in this work was as follows: About one gram of nodular material was removed aseptically from the spleen and emulsified in a sterile mortar with 5 or 6 cc. of sterile distilled water. The emulsion was filtered through sterile gauze and two guinea pigs and two rabbits inoculated with the filtrate, each guinea pig receiving 1 cc. subcutaneously and each rabbit 0.5 cc. intravenously. Five or six weeks after inoculation, each animal was tested intracutaneously with avian and mammalian tuberculins. An area several inches square on the belly of each animal was clipped and shaved and 0.05 cc. each of avian and mammalian tuberculins injected about 1.5 inches apart. The tuberculins used were prepared by the Biochemic Division of the Bureau and each cubic centimetre contained the equivalent of 0.25 gram of Koch's Old Tuberculin. Several tubes of modified Löwenstein's medium were inoculated with sections of infected tissue from each animal dying and, when colonies appeared, transfers were made to serum agar medium for cultural differentiation.

Results of the typing tests: Of the 36 specimens, 21 were shown to be of avian type of tuberculous infection and 15 of bovine type. In each state were found both avian and bovine infection. The results of the three typing methods were in complete accord.

During the typing of these swine lesions, several interesting observations were made: first, that tuberculosis in rabbits does not follow a similar course in avian and bovine infection when the inoculation is made intravenously with small numbers of tubercle bacilli; second,

that in the guinea pig the sensitization method of differentiating avian from bovine infection can be used with accuracy and a saving of time, that the sensitization method of typing cannot be used in rabbits since in this species sensitization is relatively inconstant and not specific in all cases, and that dual infection, that is, simultaneous infection with avian and bovine tubercle bacilli, may be detected by the sensitization method. A deduction will also be made as to the possible bearing of avian tuberculosis on man as a result of the apparent increase in hosts of the avian tubercle bacillus. These observations will be referred to in separate papers.

## SUMMARY

It has been known for a number of years that a great majority of the retentions of swine for tuberculosis in federally inspected abattoirs were the result of infection with avian tubercle bacilli, but this type of infection was thought to be of a nonprogressive nature and confined chiefly to the lymph nodes of the alimentary tract.

In 1936 Feldman found 24 of 30 swine carcasses condemned for generalized tuberculosis in an abattoir in Minnesota to be affected with the avian type of infection.

This report covers the typing of lesions in 36 swine condemned for tuberculosis in five of the North Central States; 21 of the specimens were found to be affected with the avian type of tubercle bacilli and 15 with the bovine type.

## REFERENCES

*See References at end of fourth article of this series.*

# STUDIES IN AVIAN TUBERCULOSIS[1]

## 2. Comparative Virulence of Avian and Bovine Tubercle Bacilli for Rabbits and Guinea Pigs

A. B. CRAWFORD

In the preceding paper, mention was made of the typing in guinea pigs and rabbits of 36 specimens of tuberculous lesions from swine condemned for generalized tuberculosis. Of the 36 specimens, 21 were found to harbor avian tubercle bacilli and 15 bovine.

In this paper will be described the comparative virulence of small numbers of avian and bovine tubercle bacilli for rabbits and guinea pigs as observed in the typing tests.

Two guinea pigs and two rabbits were inoculated with suspensions of each specimen, the guinea pigs receiving 1 cc. subcutaneously and the rabbits 0.5 cc. intravenously.

In table 1 are shown the numbers of acid-fast microörganisms found in each of the 36 suspensions. Since a 2 mm. loopful of 0.000,1 mgm. of avian tubercle bacilli suspended in 1 cc. distilled water, spread over an area about 1.5 cm. in diameter, approaches the end point where acid-fast microörganisms can be demonstrated in ten minutes' search, it will be apparent that the numbers of tubercle bacilli in these suspensions were exceedingly few in comparison to the numbers in standard typing tests where 1 mgm. and 0.01 mgm. respectively are used. This point is emphasized in connection with the susceptibility of the rabbit to avian and bovine tubercle bacilli in minute doses.

*Results in guinea pigs:* In guinea pigs, bovine tuberculosis could be detected within a few weeks by the appearance of an open lesion at the site of inoculation, by an enlargement of the inguinal lymph node adjacent to the site of injection, and later by emaciation and death within two to four months from generalized tuberculosis.

A few of the guinea pigs in avian infection showed a small open lesion. Of 8 that were killed for cultural purposes within two or three months, 4 showed a very slight enlargement of the adjacent inguinal lymph node

[1] From the Animal Disease Station, Beltsville, Maryland, Bureau of Animal Industry, United States Department of Agriculture.

in the centre of which, on incision, a minute area of yellow necrosis or a droplet of yellowish pus was observed. No other lesion was observed except in one instance a very slight thickening of the spleen. None of the guinea pigs in the avian series died of tuberculosis. About six months after inoculation, the 34 surviving were killed and in only 4 was a lesion found, in each case being a slightly swollen inguinal lymph node with a centrally located yellowish granular area. In each of these

TABLE 1

*Showing the number of acid-fast microörganisms found in suspensions prepared from lesions in swine condemned for generalized tuberculosis, used in inoculating guinea pigs and rabbits. Five to 15 minutes' search was made of each preparation*

| AVIAN TYPE INFECTION | | BOVINE TYPE INFECTION | |
|---|---|---|---|
| Specimen number | Number of acid-fasts found | Specimen number | Number of acid-fasts found |
| 1 | 8 | 2 | 2 |
| 3 | 0 | 5 | 2 |
| 4 | 6 | 6 | 0 |
| 9 | 6 | 7 | 0 |
| 11 | 2 per field | 8 | 0 |
| 12 | 2 | 10 | 1 |
| 15 | 0 | 13 | 0 |
| 16 | 0 | 14 | 0 |
| 21 | 4 | 17 | 0 |
| 22 | 2 per field | 18 | 0 |
| 24 | 6 | 19 | 0 |
| 25 | 4 | 20 | 0 |
| 27 | 10 | 23 | 0 |
| 28 | 6 | 26 | 0 |
| 29 | 0 | 32 | 1 |
| 30 | 1 | | |
| 31 | 0 | | |
| 33 | 3 | | |
| 34 | 0 | | |
| 35 | 0 | | |
| 36 | 0 | | |

four cases, smear preparations showed faintly staining acid-fast bodies, some whole and others in various stages of degeneration.

*Results in rabbits:* In rabbits, interesting observations were made relative to the respective virulence of avian and bovine tubercle bacilli and the course of the disease caused by these two types of tubercle bacilli.

In this investigation the bovine tubercle bacillus was shown to be decidedly more virulent for the rabbit than the avian tubercle bacillus.

Thirty rabbits were inoculated with swine tissue lesions later proved to be caused by the bovine tubercle bacillus. Three died within one week, one died of enteritis 46 days after inoculation showing slight lesions of tuberculosis, and all of the remaining 26 rabbits died of tuberculosis within a period of 43 to 99 days, the average length of survival being slightly more than 70 days. This corresponds very closely to the virulence of the bovine tubercle bacillus for guinea pigs on subcutaneous inoculation.

Forty-two rabbits were inoculated with swine tissue lesions caused by the avian tubercle bacillus. Three died within one week and, of the 39 remaining, only 9 died of tuberculosis before the 99th day following inoculation. Eight others died of tuberculosis between the 116th and 178th days after inoculation. One rabbit died on the 40th day showing extreme emaciation but no visceral alteration or tuberculous involvement was apparent. Two rabbits died of intercurrent infection during the 99-day period showing lesions of tuberculosis but insufficient to warrant expectancy of death within this period, and 2 others died of intercurrent infection, 138 and 191 days after inoculation, respectively, in each only slight lesions of tuberculosis being observed. Six rabbits of this series were killed between the 73rd and 98th day after inoculation for cultural purposes. One showed no macroscopical tuberculous involvement but one tube of medium inoculated with the apparently normal spleen of this animal developed 43 colonies of characteristic avian growth. The other 5 rabbits showed tuberculous involvement but not sufficiently progressive to warrant expectancy of death for several weeks to possibly several months. The remaining rabbits in this series were killed between the 101st and 219th day following inoculation, for cultural purposes or to close out the experiment. Slight to well marked lesions of tuberculosis were observed in all but one, the latter having apparently escaped infection. This animal was the mate of the one previously mentioned as being killed and showing no lesions, yet harboring avian tubercle bacilli in the apparently normal spleen. Specific reference is made of this as reference will hereinafter be made to the fact that the two guinea pigs inoculated with the same swine lesion material developed a sensitization to avian tuberculin.

It will be noted from table 1 that, as a whole, more acid-fast bacilli were found in the avian series of swine lesions than in the bovine series.[2]

[2] The fact that more avian tubercle bacilli were found in these suspensions than bovine tubercle bacilli opens a field for speculation as to whether avian tubercle bacilli are more

It is believed that the data show conclusively that the rabbit has practically no resistance to the intravenous injection of the bovine type of tubercle bacillus. To the avian type of the tubercle bacillus, the rabbit, as the data show, exhibits a susceptibility but there is manifest a variable resistance to the rapidity of the generalization of the disease.

The more manifest susceptibility of the rabbit to the bovine tubercle bacillus, when small numbers of tubercle bacilli are injected intravenously, is demonstrated chiefly in the major localization in the lungs by the bovine tubercle bacillus in contradistinction to a minor localization in this organ by the avian tubercle bacillus (see table 2). The only lesions

TABLE 2

*Showing the comparative distribution of lesions in the lungs, spleen, liver, and kidneys of rabbits resulting from the intravenous injection of suspensions of tuberculous swine lesions*

| NUMBER OF RABBITS EXAMINED | TYPE OF INFECTION | LESIONS IN | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Lungs | | | | Spleen | | | | Liver | | | | Kidney | | | |
| | | Extensive | Well-marked | Slight | Total affected | Extensive | Well-marked | Slight | Total affected | Extensive | Well-marked | Slight | Total affected | Extensive | Well-marked | Slight | Total affected |
| 38 | Avian | 0 | 6 | 17 | 23 | 12 | 7 | 7 | 26 | 4 | 3 | 13 | 20 | 1 | 3 | 18 | 22 |
| 26 | Bovine | 26 | 0 | 0 | 26 | 7 | 9 | 8 | 24 | 1 | 9 | 11 | 21 | 3 | 12 | 9 | 24 |
| | | *Percentages* | | | | | | | | | | | | | | | |
| 38 | Avian | 0 | 16 | 44 | 60 | 32 | 18 | 18 | 68 | 11 | 8 | 34 | 53 | 3 | 8 | 47 | 58 |
| 26 | Bovine | 100 | 0 | 0 | 100 | 27 | 34 | 31 | 92 | 4 | 35 | 42 | 91 | 12 | 46 | 34 | 92 |

observed in the rabbits in this series and not mentioned in table 2 were in two animals which showed clusters of minute tuberculous foci on the intestinal serosa.

In contrast to the extensive affection of the lungs of the rabbits in the bovine series, the lungs of the rabbits in the avian series showed comparatively slight involvement. These lesions consisted of scattered yellowish-white encapsulations up to 3 mm. in diameter, mostly under

resistant to the destructive forces of the body than bovine, but are less toxic (Lurie). The tubercles in the spleens of swine in the bovine series invariably showed marked necrosis, whereas in only one specimen in the avian series was marked necrosis apparent macroscopically. In this connection, Sabin and Smithburn have noted that avian phosphatide is less readily emulsified by monocytes than bovine phosphatide.

the pleura. In a few animals, the visceral pleura along the margin of the lung showed grayish necrotic areas which in some instances extended a few millimetres into the lung tissue. Another salient point, in connection with avian infection in the rabbit, was the variation in the chief site of tuberculous localization. The spleen was most often the chief site of localization. The character of the lesions in the spleen varied, in some instances the organ having a smooth, swollen appearance, with no visible tuberculous foci, while in others the parenchyma manifested whitish encapsulations up to 2 mm. in diameter. The earliest joint tuberculosis observed in this series was 145 days after inoculation. Nine rabbits showed such lesions, 7 being classed as extensive, 1 as well-marked, and 1 as slight. Six rabbits showed clusters of tuberculous pearls on the intestinal serosa or peritoneum. One rabbit showed clusters of minute, whitish, tuberculous foci, about one inch wide and four inches in length on the subcutem of the belly. Two rabbits showed tuberculous involvement of the spinous processes of the lumbar vertebrae. One rabbit showed numbers of minute whitish foci in the bone marrow and stained smears of the marrow showed several hundred acid-fast microörganisms per microscopical field.

One of the most interesting observations in connection with avian infection in rabbits was the presence under the serosa of the ileocaecal valve and the tip of the caecum of minute, whitish necrotic foci, pinpoint in size up to 2 mm. in diameter. In the rabbit, the ileocaecal valve is a bulbous enlargement of the ileum at its junction with the caecum and the caecum is a blind gut about 18 inches long, tapering and sacculated up to within two to three inches of its blind end where the tissue takes on a smooth, lymphoidal appearance. Tubercle bacilli can be demonstrated in the foci in these sites. Eighteen of the rabbits in this series showed these minute, whitish foci under the serosa of the ileocaecal valve and the tip of the caecum, the number of foci usually varying from 5 to 25 but in some instances the entire surface of these sites was peppered. Usually more were found on the valve than on the tip of the caecum. Unfortunately this observation was not made until a number of the rabbits in the avian series and all in the bovine series had been examined. Lurie (personal communication) states that similar lesions occur also in chronic bovine infection. In those rabbits examined postmortem subsequent to 100 days after inoculation, lesions were found in these sites in all but two instances. One animal, killed

219 days after inoculation, showed lesions in each of these sites and the only other lesion observable was in one knee joint.

## SUMMARY

In a series of 42 rabbits inoculated intravenously with suspensions of the avian type of tuberculous tissue from swine and a series of 30 rabbits inoculated with similar suspensions of the bovine type of infection in swine, the bovine tubercle bacillus was shown to be decidedly more virulent for the rabbit than the avian type.

In the bovine series, 100 per cent of the rabbits died of tuberculosis within 99 days, whereas, in the avian series, only 23 per cent died within this period.

In the bovine series, the lungs were the chief site of localization while in the avian series the lungs were only relatively slightly affected and the chief site of localization was variable.

# STUDIES IN AVIAN TUBERCULOSIS[1]

## 3. Sensitization Method of Differentiating Avian from Bovine Infection in Guinea Pigs and Rabbits

A. B. CRAWFORD

In 1927, the author (5) described the sensitization method of differentiating avian from mammalian tubercle bacilli. Briefly, this consists of injecting tuberculous animals with avian and mammalian tuberculins, the tuberculin homologous to the type of the infecting microörganism invariably causing the greater reaction. By its application to the bacillus Calmette-Guérin (BCG), this microörganism was shown to be of mammalian type.

This method is used in typing tests at this Station where most of the tuberculous specimens examined are either of avian or bovine type and the considerable experimentation done in this connection has shown that the method is specific. Its application in the investigation of tuberculosis in swine, mentioned in the first paper in this series, is herewith described.

About six weeks after inoculation with swine tissue suspension, each of the guinea pigs and rabbits was tested intracutaneously with avian and mammalian tuberculins. The reactions were recorded at the 48th hour.

In rabbits, the reactions seldom showed definition, being characterized by an erythema, usually mild, surrounding the area into which the tuberculin was injected, with a slight thickening of the skin. In no instance was there central necrosis. Some animals failed to react to either tuberculin. It may be stated that the reactions, as a whole, were more marked to the homologous tuberculin, but in some rabbits the difference was not marked and in one instance in avian infection, one of the rabbits showed more reaction to mammalian tuberculin than to avian. The inconstancy in the manifestation of specific and nonspecific sensitization in the rabbit rules out the usefulness of this species for the sensitization method of differentiation.

[1] From the Animal Disease Station, Beltsville, Maryland, Bureau of Animal Industry, United States Department of Agriculture.

TABLE 3

*Showing reactions to avian and mammalian tuberculins respectively in guinea pigs injected with lesions from swine condemned for generalized tuberculosis. For the sake of brevity, only the first five of each type are shown*

| SPECIMEN NUMBER | GUINEA PIG NUMBER | KIND OF TUBERCULIN INJECTED | REACTIONS | | | | TYPE OF INFECTION |
|---|---|---|---|---|---|---|---|
| | | | Diameter in millimetres | Thickness of skin | Erythema | Central necrosis | |
| 1 | 1 | Avian | 17 | xxx | xxx | 6 x 10 | Avian |
| | | Mammalian | 6 | x | x | None | |
| | 2 | Avian | 13 | xxx | xxx | 5 x 9 | |
| | | Mammalian | 8 | xx | None | None | |
| 2 | 3 | Avian | 9 | xx | xx | None | Bovine |
| | | Mammalian | 35 | xxx | xxx | 7 x 12 | |
| | 4 | Avian | None | 0 | 0 | None | |
| | | Mammalian | 18 | xxx | xxx | 10 x 12 | |
| 3 | 5 | Avian | 15 | xxx | xxx | 4 x 6 | Avian |
| | | Mammalian | 5 | x | x | None | |
| | 6 | Avian | 20 | xxx | xxx | 4 x 10 | |
| | | Mammalian | 10 x 12 | xx | xx | None | |
| 4 | 7 | Avian | 12 x 15 | xx | xx | 2 | Avian |
| | | Mammalian | None | 0 | 0 | None | |
| | 8 | Avian | 10 | xx | xx | 3 | |
| | | Mammalian | 7 | xx | x | None | |
| 5 | 9 | Avian | None | 0 | 0 | None | Bovine |
| | | Mammalian | 12 x 15 | xxx | xxx | 10 x 12 | |
| | 10 | Avian | None | 0 | 0 | None | |
| | | Mammalian | 14 x 20 | xxx | xxx | 10 x 13 | |
| 6 | 11 | Avian | 4 | x | x | None | Bovine |
| | | Mammalian | 14 | xxx | xxx | 10 | |
| | 12 | Avian | 8 | xx | 0 | None | |
| | | Mammalian | 15 | xxx | xxx | 8 | |
| 7 | 13 | Avian | None | 0 | 0 | None | Bovine |
| | | Mammalian | 14 x 20 | xx | xx | 8 x 10 | |
| | 14 | Avian | None | 0 | 0 | None | |
| | | Mammalian | 18 | xxx | xxx | 11 | |
| 9 | 15 | Avian | 9 x 12 | xx | xxx | 4 | Avian |
| | | Mammalian | None | 0 | 0 | None | |
| | 16 | Avian | 11 | xxx | xxx | 3 | |
| | | Mammalian | 7 | xx | xx | None | |

TABLE 3—*Concluded*

| SPECIMEN NUMBER | GUINEA PIG NUMBER | KIND OF TUBERCULIN INJECTED | REACTIONS | | | | TYPE OF INFECTION |
|---|---|---|---|---|---|---|---|
| | | | Diameter in millimetres | Thickness of skin | Erythema | Central necrosis | |
| 10 | 17 | Avian | 0 | 0 | 0 | None | Bovine |
| | | Mammalian | 15 x 20 | xxx | xxx | 4 x 9 | |
| | 18 | Avian | 0 | 0 | 0 | None | |
| | | Mammalian | 14 x 18 | xxx | xxx | 3 x 7 | |
| 11 | 19 | Avian | 12 x 15 | xxx | xxx | 7 x 9 | Avian |
| | | Mammalian | 11 x 13 | xxx | xxx | None | |
| | 20 | Avian | 12 x 16 | xxx | xxx | 4 x 7 | |
| | | Mammalian | 6 x 9 | xx | xx | None | |

Explanation of symbols: x indicates slight
xx indicates average
xxx indicates extensive

In guinea pigs, however, the results were remarkably clean cut and differentiable. In every instance, the reactions in guinea pigs definitely indicated avian or bovine infection (see table 3). At the 24th hour, reactions were evident and consisted of a diffuse inflammation of the skin over the injected area from less than one to several centimetres in diameter, with a beginning central necrosis or blanching on the side where the homologous tuberculin was injected. The differences in the reactions to the two tuberculins were not so well marked at this period. At the 48th hour, when the final reading was made, the reactions reached their maximum definition; on the side where the homologous tuberculin was injected, the skin was thickened giving it a "plateau" or mounded appearance, the central portion showed a clearly defined area of yellowish necrosis, and surrounding this an erythematous zone with well defined margins. The reaction to the heterologous tuberculin, when present, had the same general appearance with the exceptions that the area involved was smaller, the erythema less intense, and there was no central necrosis. The reaction to avian tuberculin in avian infection was not as voluminous as the reaction to mammalian tuberculin in bovine infection which would naturally be expected since bovine tuberculosis in guinea pigs is a progressive disease and the sensitization increases with the extension of the lesions until the animal shows loss of condition. In table 3 are shown the results of typing tests in guinea pigs sensitized by swine tissue suspensions, five each of avian and bovine infection.

That the guinea pig which is naturally immune to the avian type of tubercle bacillus should show such a high degree of sensitization, especially in view of the small numbers of tubercle bacilli present in most of the suspensions (see table 1), seems truly remarkable. In order to obtain information as to the relative numbers of avian tubercle bacilli necessary to cause a sensitization to avian tuberculin in guinea pigs, an experiment was made in which groups of guinea pigs were injected subcutaneously with serial dilutions of a suspension of young, virulent avian tubercle bacilli. Two guinea pigs received each 0.1 mgm. in one cc. of diluent, two, 0.01 mgm., and so forth until the last two received 0.000,001 mgm. It was found that the smallest dose constantly capable of causing sensitization was between 0.000,1 and 0.000,01 mgm. of avian tubercle bacilli. In one guinea pig, 0.000,001 mgm. caused a sensitization to tuberculin.

Accepting that there are one billion avian tubercle bacilli in one milligram of moist culture, it would therefore appear that about 10,000 avian tubercle bacilli are necessary to sensitize a guinea pig to avian tuberculin. In many of the swine tissue suspensions it was impossible to demonstrate acid-fast microörganisms in smear preparations, and this brings up the question as to whether or not tubercle bacilli in animal tissues are more capable of sensitizing than those grown on culture media. In this connection, it was observed in smear preparations of swine, guinea pig, and rabbit tuberculous lesions, that many acid-fast microörganisms showed the presence of dark-staining granules, usually polar but sometimes centrally or eccentrically located. These granules, almost a bluish-black, were often half again the thickness of the bacillus and similar bodies were observed free. When slightly out of focus, these granules are refractile, changing from a bluish-black to a red color. The nature of these dark-staining granules is intriguing and suggests that they may be a resting or resistant form of the tubercle bacillus. A stained smear from a joint lesion in a rabbit affected with avian tuberculosis showed approximately 30 per cent of the acid-fast bacilli with these dark-staining granules and a culture from this lesion on modified Löwenstein's medium showed between 500 and 600 colonies, barely macroscopical but easily seen with a hand lens, in six days' time. These colonies consisted of extremely minute acid-fast microörganisms and later manifested the typical appearance of cultures of avian tubercle bacilli. The presence of the granular form of the tubercle bacillus in

tissues may explain the sensitization of guinea pigs by tissue suspensions even though acid-fast bacillary forms cannot be demonstrated.

*Application of the sensitization method of typing in mixed or dual infection with avian and bovine tubercle bacilli:* In the 36 specimens of swine tuber-

TABLE 4

*Results of the application of the sensitization method in dual infection with avian and bovine tubercle bacilli, with control groups*

| | GUINEA PIG | AVIAN TUBERCULIN | MAMMALIAN TUBERCULIN |
|---|---|---|---|
| Avian tubercle bacillus infection only | 59885 | 13 mm. T., v.i. 3 x 5 c.n. | 7 mm. S.T., no i. |
| | 59886 | 12 mm. T., v.i. 3 x 4 c.n. | 7 mm. node, s.i. |
| Bovine tubercle bacillus infection only | 59883 | 8 mm. node, s.i. | 20 mm. T., i. |
| | 59884 | 12 mm. T., s.i. | 20 mm. V.T., v.i. 12 c.n. |
| Mixed avian and bovine tubercle bacilli in one site | 59887 | 12 x 13 V.T., v.i. 4 x 7 c.n. | 18 mm. V.T., v.i. 8 x 11 c.n. |
| | 59888 | 10 x 12 mm. T., i. 3 x 7 c.n. | 26 mm. V.T., v.i. 15 mm. c.n. |
| | 59889 | 10 x 12 mm. T., i. 6 x 9 c.n. | 25 mm. V.T., v.i. 14 mm. c.n. |
| | 59890 | 10 mm. T., i. | 18 x 20 mm. V.T., v.i. 8 mm. beginning c.n. |
| Avian tubercle bacilli in right thigh and bovine tubercle bacilli in left thigh | 59891 | 10 mm. node, s.i. | 30 mm. V.T., v.i. 10 x 12 c.n. |
| | 59892 | 14 mm. T., i. 5 mm. c.n. | 12 x 20 mm. V.T., v.i. 10 mm. c.n. |
| | 59893 | 12 x 15 mm. T., i. 4 x 7 mm. c.n. | 30 mm. V.T., v.i. 15 x 18 mm. c.n. |
| | 59894 | 11 mm. T., i. | 20 mm. V.T., v.i. no necrosis but 4 x 7 central blanching |

Explanation of symbols:

T.—skin moderately thickened
S.T.—skin slightly thickened
V.T.—skin very thickened
i.—moderately inflamed
s.i.—slightly inflamed
v.i.—very inflamed
c.n.—central necrosis

culosis, described in this investigation, each was definitely of avian or bovine type. Of 209 specimens of swine tuberculosis examined by Van Es and Martin (1), 13 (6.22 per cent) were found to contain both

avian and bovine types of tubercle bacilli. The same authors (6) report 4 cases (3.48 per cent) of mixed infection with avian and bovine tubercle bacilli in 115 cases of lymph node tuberculosis in bovine animals. It is quite possible, therefore, if further typing of swine tuberculosis is done, dual infection with avian and bovine tubercle bacilli will be encountered.

In order to throw light on the efficacy of the sensitization method of typing such dual infection, an experiment was made in which guinea pigs were sensitized with avian and bovine tubercle bacilli and later tested with avian and mammalian tuberculins. The methods of treatment and the results of the tuberculin tests are shown in table 4.

The results in these experimental animals were not so clear cut as in individual sensitization, but it is believed that the dual type of infection can be detected by one practiced in reading tuberculin reactions. The criteria of dual infection would be well marked reactions with central necrosis to both avian and mammalian tuberculins and the reaction to mammalian tuberculin slightly more voluminous than that to avian tuberculin.

## SUMMARY

The sensitization method of differentiating avian from bovine infection in swine tuberculosis is shown to be specific. Of 36 specimens, 21 caused in guinea pigs a sensitization specific to avian tuberculin and 15 to mammalian tuberculin. These figures were in complete agreement with the animal inoculation test and culture typing. The results of an experiment are shown which indicate that dual infection with avian and bovine tubercle bacilli may be detected by the sensitization method.

## REFERENCES

*See References at end of fourth article of this series.*

# STUDIES IN AVIAN TUBERCULOSIS[1]

## 4. The Possible Rôle of the Avian Tubercle Bacillus in Infection in Man

A. B. CRAWFORD

The discovery by Griffith (7) and Cumming (8) that the bovine type of tubercle bacillus is capable of causing generalized disease in man, the report of Harshfield and Roderick (9) and similar case records of the Bureau of Animal Industry of the finding of avian tubercle bacilli in generalized tuberculosis in sheep, a species of animal in which tuberculosis is extremely uncommon, and the recent discovery by Feldman (4) that the avian type of tubercle bacillus is capable of causing generalized disease in swine, might lead one to suspect that the various types of tubercle bacilli may be gradually assuming an increased virulence for those species of animals which were considered naturally immune, or, at least, very resistant to the respective types.

"Species immunity" is usually a relative rather than a constant factor, since in many species highly resistant to various types of tubercle bacilli certain individuals may develop lesions of a type of tuberculosis heterologous to the animal species. The reverse order obtains in "susceptible species" where a majority will contract tuberculosis if given a certain amount of exposure while certain individuals of the same species exhibit a marked or total resistance to an equal degree of exposure.

Another factor which undoubtedly operates in heterologous tuberculosis, and to a lesser degree in homologous tuberculosis, is continuous or frequently repeated exposure over a long period of time. For instance, the relatively high incidence of the bovine type of infection in man in the British Isles can be associated with the high incidence of tuberculosis in cattle. It has been variously estimated that 25 to 50 per cent of the dairy cattle of England and Scotland are affected with tuberculosis and, amazingly, these percentages have not varied much during the last 25 or 30 years. With such a high incidence of bovine tuberculosis, it is quite evident that a large portion of the milk must be contaminated with bovine tubercle bacilli. Pasteurization of milk does not seem to

[1] From the Animal Disease Station, Beltsville, Maryland, Bureau of Animal Industry, United States Department of Agriculture.

have been as readily adopted there as in this country, and the result has been that many consumers of milk have frequently and over considerable periods been exposed to virulent bovine tubercle bacilli.

In this country, avian tuberculosis has gained a definite foothold, especially in the North Central States. Surveys made in townships in some of these states reveal the fact that as high as 80 per cent of poultry flocks show infection. It is apparent that animals cohabiting on such infected premises must suffer frequent and repeated exposure to avian tubercle bacilli. An investigation made at this Station many years ago during the "bovo-vaccination" period, when experiments were being made in the use of the human tubercle bacillus in the vaccination of cattle against bovine tuberculosis, supports the possibility of danger from repeated exposures to a heterologous type of tubercle bacilli. During this investigation, cattle were injected intravenously with cultures of human tubercle bacilli; those receiving one dose suffered no ill effects and no lesions were observed when the animals came to autopsy; those receiving two injections showed scattered nodules in the lungs on postmortem examination; those receiving three injections showed extensive lung lesions and scattered lesions in other organs; those receiving four injections became fatally affected with tuberculosis. This experiment has always seemed to the author to present very strong evidence of the danger of the oft repeated infection. It shows that natural immunity may be broken down, and it seems plausible to believe that the production of allergy by the initial exposure plays a rôle similar to that of the childhood type of tuberculosis in man in its relation to subsequent infection.

Whether or not avian tuberculosis presents a danger to man is a moot question. Meat of poultry is not ingested by man in a raw state. Eggs laid by hens affected with tuberculosis of the oviduct have been found to be contaminated with virulent avian tubercle bacilli, but only a small portion of the eggs from tuberculous flocks contain tubercle bacilli. Virulent tubercle bacilli are found more frequently in fresh than in storage eggs. The boiling of eggs, unless the yolk is thoroughly congealed, does not assure the killing of tubercle bacilli. It is conceivable that if contaminated eggs were ingested raw or only partially cooked, especially by persons of lowered resistance in whom such a practice might be prescribed, and continued over a period of time, it might lead to the tuberculization of such persons with the avian type of tubercle bacillus. Feldman (10) has shown that virulent avian tubercle bacilli are some-

times present in the apparently normal superficial lymph nodes of swine showing lesions in visceral nodes, and if such superficial nodes, apparently normal but harboring virulent avian tubercle bacilli, were incorporated in uncooked sausages, they would present another possible source of infection with this microörganism. Dressers in poultry-killing establishments come more or less in contact with avian tubercle bacilli in handling the viscera of tuberculous birds. Persons tending tuberculous poultry undoubtedly suffer the greatest exposure to avian tubercle bacilli, not only by possible ingestion but also by inhalation of dust in contaminated chicken houses. The continuous scratching of straw and other litter by poultry pulverizes contaminated faecal matter and the dust thus raised is very apt to carry virulent tubercle bacilli. If avian tuberculosis is capable of becoming a menace to the health of man, it should be demonstrable in individuals in this group.

It would seem from the exceedingly few cases of tuberculosis in man that have been ascribed to the avian tubercle bacillus that man is very resistant to this type of infection or that the amount of exposure offered is insufficient to cause infection except in extremely rare instances.

However, if tuberculosis in poultry continues to increase as rapidly as it has in the last two decades, it will not be without danger to those human beings, at least, who are least resistant to this type of tuberculous infection. This possibility, although remote, adds a further argument to those already existing for the inauguration of a definite program leading to the control of avian tuberculosis.

## SUMMARY AND CONCLUSIONS

The few proved cases of avian type of tuberculous infection in man indicate that the human species is very resistant to this type of infection or that the amount of exposure is insufficient to cause disease except in rare instances.

Persons tending tuberculous flocks suffer the greatest exposure, not only by possible ingestion but also by inhalation. The chief manner in which the general population may be exposed is through the ingestion of eggs from hens affected with tuberculosis of the oviduct. If tuberculosis in poultry were to become so widespread as to increase the frequency of man's exposure, it is conceivable that it might not be without danger to those individuals who are least resistant.

In the light of present evidence, however, it does not seem that the

avian type of tuberculosis presents more than a remote possibility of danger to man.

The appreciation of the author is hereby expressed to Dr. Arnold R. Rich, of Johns Hopkins University, to Dr. William H. Feldman, of the Mayo Foundation, and to Dr. Max B. Lurie, of the Henry Phipps Institute, for their kind suggestions in connection with the preparation of these papers.

## REFERENCES

(1) VAN ES, L., AND MARTIN, H. M.: An inquiry into the cause of the increase of tuberculosis of swine, Research Bulletin 30, University of Nebraska Agricultural Experiment Station, 1925.

(2) STEIN, C. D.: Human and avian types of tubercle bacilli recovered from swine, Jour. Amer. Vet. Med. Assn., 1933, *36*, 105.

(3) CRAWFORD, A. B.: Two unusual cases of tuberculosis in hogs caused by the avian type of tubercle bacillus, Ibid., 1933, *36*, 110.

(4) FELDMAN, W. H.: Report of the special committee on tuberculosis, Ibid., 1936, *42*, 456. (Complete report on 30 cases to be published J. A. V. M. A.)

(5) CRAWFORD, A. B.: A sensitization method of differentiating avian from mammalian tubercle bacilli, Amer. Rev. Tuberc., 1927, *15*, 111.

(6) VAN ES, L., AND MARTIN, H. M.: Incidence of avian tuberculosis in mammals other than swine, Research Bulletin 49, University of Nebraska Agriculture Experiment Station, 1930.

(7) GRIFFITH, A. S.: Observations on bovine tubercle bacillus in human tuberculosis, Brit. Med. Jour., 1932, *2*, 501.

(8) CUMMING, W. M.: The type of the causal organism in 1,502 recent English and 320 recent Irish cases of pulmonary tuberculosis, Tubercle, 1935, *17*, 67.

(9) HARSHFIELD, G. S., AND RODERICK, L. M.: Avian tuberculosis in sheep, Jour. Amer. Vet. Med. Assn., 1934, *38*, 597.

(10) FELDMAN, W. H.: Recovery of virulent tubercle bacilli from the tissues of swine intended for food, Jour. Infec. Dis., 1936, *59*, 43.

# THE EFFECT OF HUMAN TISSUE JUICES ON TUBERCLE BACILLI[1]

NELL HIRSCHBERG AND LLOYD ARNOLD

Certain investigators have concluded that various parts of the human body were not susceptible to tuberculous infection. The thyroid, pancreas, and even the brain were considered to be relatively immune (although it was known, of course, that the meninges could be infected). A review of the literature, however, convinces one that although the incidence of infection of these and other organs is certainly very low, they are not immune to tuberculosis. Various reasons have been advanced for the apparent selection of certain organs by the tubercle bacillus, and, although the problem has received attention since the late nineteenth century, it has never been entirely solved.

Nolan (1932) and Brines (1932) have shown the variations in the distribution of tuberculous infection in the human body from autopsy findings.

Most of the investigations in this field have been concerned with such reasons for organ specificity as racial immunity, species immunity, point of entrance of the infecting microörganism, methods of dissemination of the bacilli, as well as such local factors as food supply, cellular immunity, physical and chemical properties, or bactericidal substances in the tissues.

Pinner (1937) has adequately summarized the findings of investigators reporting on racial immunity to tuberculosis as follows: "No single factor can explain or has sovereign importance in the epidemiological and pathogenic behavior of tuberculosis. While it seems likely that race is one of these factors, it is certain that living conditions in the broadest sense of the word are of great importance and that many other factors, known and unknown ones, determine the course of events."

The portal of entry is of course known to be one of the greatest factors in pulmonary tuberculosis. Apparently, however, the specific point of entry does not necessarily determine the site of tuberculous infection

[1] From the Department of Bacteriology and Public Health, University of Illinois, College of Medicine, and Michael Reese Hospital, Chicago, Illinois.

in the human body. Cameron (1934) demonstrated that tubercle bacilli may pass through the mucous membranes without leaving any sign at the point of entry.

Most investigators agree that the haematogenous spread of tubercle bacilli accompanied by the less important lymphatic route accounts for the dissemination of tuberculosis in the human body. In spite of this, however, tuberculous bacillaemia was found by Wilson (1932) to be usually uncommon except in advanced and progressive tuberculosis. Miller (1936) stated that tubercle bacilli may be disseminated by lymph or blood-stream from the primary complex and may reach any organ, but invariably reach the lungs. It can be concluded that blood has but little effect on the tubercle bacillus. It acts merely as a carrier agent.

The metabolic requirements of tubercle bacilli have been well known for many years. Long (1930) stated that human tissues may not satisfy all of their requirements, may have too high a temperature or the wrong reaction for the growth of the microörganism, but that in general the body is able to supply the needs of the microörganism.

Nonspecific factors such as chemical and physical properties and bactericidal properties of tissues have received a great deal of experimental investigation. Porter (1917), one of the early authors to investigate this problem, made glycerin extracts of certain organs for esterases. He studied pancreas, liver, kidney, spleen, lung, skin, suprarenals and lymph nodes. He stated that if the extracts contained a high esterase content they dissolved tubercle bacilli. This action he termed "bactericidal." He found the lung the least "bactericidal" and the pancreas the most "bactericidal," although liver, thymus and lymph nodes possessed moderate amounts of lytic power. These results have been quoted in most textbooks on tuberculosis.

Erba (1933) stated that the experimental evidence was not sufficient to establish the existence of a bactericidal substance, reaction of which was specific against tuberculosis.

There have been few investigations, other than those previously stated, of the presence or absence of growth inhibiting or growth enhancing substances for the tubercle bacillus in the various organs of the human body.

This paper represents an experimental attempt to determine the presence or absence of such substance in various organs of the human body and in this way to shed some light on organ specificity in tuberculosis.

## EXPERIMENTAL PROCEDURE

The basic medium used was described in a recent report by Seibert (1934) and gives a very heavy growth. It contains no organic material.

Fifteen cubic centimetres of this basic medium were sterilized in small wide-mouthed vaccine bottles and tissue juice was added to give final percentages of 2, 4, 6, 8, 10 and 20 per cent. Additional bottles contained undiluted tissue juice and other bottles, the controls, medium without tissue juice.

Tissue was obtained from fresh organs of normal healthy individuals who had died by accident or gun-shot wounds. All the organs examined were from white adult males between the ages of thirty-five and forty-five. Most of the individuals from whom organs were taken showed evidence of a primary focus of tuberculosis in the lungs, but were free from foci elsewhere and showed no evidence of active disease. All appeared to be in good health with no indications of abnormal metabolism or systemic disease of any kind. The individuals from whom lung tissue was taken showed no focus of tuberculosis in that portion of the organ selected.

The cause of death of those individuals from whom organs were taken was accidental and not related in any way to disease. Through the coöperation of the coroner, the organs were removed from the body as soon as possible after death, preserved on ice and used for the preparation of tissue juice as soon as possible.

The organs were removed to the laboratory and washed quickly under tap water, the excess water immediately dried with a sterile towel and the tissue cut into pieces with a long pair of shears. The fat, blood-vessels and loose connective tissue were removed and the pieces of tissue were ground in a fine meat grinder. The tissue was then subjected to one of two tissue presses—Seegal and Khorazo (1934) or Rosenow (1914). The juice was removed from the press to a sterile flask and the residue of tissue ground with sand in a mortar. This tissue mass was then centrifuged and the sediment again ground with sand in a mortar. Microscopical examination did not reveal any evidence of whole cells.

The tissue juice was passed through a Seitz filter, removed to sterile bottles, placed in the icebox and used as soon after collection as possible.

Every effort was made to work as rapidly as possible and to prepare the tissue juice quickly in order that the tissue should be as normal as possible. The hydrogen-ion concentration of the tissue juices varied

from pH 6.5 to pH 7.0, the lowest being kidney and brain; the hydrogen-ion concentration of the juices was usually about pH 6.8. Reiss and Simonin (1927) showed a substantial increase in acidity of tissue preserved after death under sterile conditions and a substantial increase in the alkalinity of tissue allowed to putrefy; apparently very little change in chemical constitution took place in the cells of the organs treated in the foregoing fashion, since the hydrogen-ion concentration of the juices remained so close to normal. In the same way any thermolabile bacteriolytic principle was not eliminated from the tissue juices.

It seems probable that these tissue juices did not contain an appreciable amount of lysozyme. It seems equally certain that they did not contain lipase or esterase.

The microörganism used for these experiments was a human strain isolated from the sputum of a patient with active pulmonary tuberculosis. Preliminary experiments showed that the virulence of this bacillus apparently had not decreased to any appreciable extent. One drop of suspension of it, approximately 0.05 cc., prepared according to the method of Tunnicliff, Howell and Hirschberg (1933), containing approximately fifty million microörganisms, was delivered onto the surface of the medium at the point where the medium was in contact with the wall of the bottle. In this way the bacilli were gently drawn over the surface in a thin, evenly distributed film. The mouths of the bottles were sealed with two cubic centimetres of melted paraffin and capped with tin foil. The bottles were removed to the incubator on a tray to prevent disturbance of the bacillary film on the surface of the medium.

The controls were allowed to attain a maximum growth. In six weeks arbitrary standards were chosen to describe the amount of growth on the surface of the medium in varying degrees. The results were recorded as plus-minus, one plus, two plus, three plus and four plus. They varied from a very faint suggestion of a film of growth (which nevertheless showed definite evidence of development of microörganisms) to a growth which was very thick, wrinkled and heavy in appearance.

The morphology of the bacilli also appeared to be perfectly normal with the usual variations in very young or very old cultures.

These cultures were used as standards for comparison with the experimental cultures and were studied during the same time intervals.

The preparation of tissue juice was a rather difficult procedure. Tissues were chosen which had been most widely investigated by other

workers, which seemed to have the most bearing on the subject, which could be easily obtained in quantity and which yielded the largest amounts of workable material. Certain small glands, therefore, were eliminated from the investigation. The following tissues were chosen: brain, heart, kidneys, liver, spleen, pancreas, thyroid, lung and blood. Certain additional experiments with commercially prepared dried tissue, tissue extract, or tissue secretion were performed in connection with the investigation of the properties of the fresh materials. It seemed wise to include experiments with blood, blood serum and blood plasma since so many investigators differed as to the effect of these substances on tubercle bacilli.

The tissue juices were subjected to varying degrees of heat and were tested for complement content, hydrogen-ion concentration, antibodies, lipase content and lysozyme content, both before and after heating. Blood serum was heated to 56°C. for two hours, the other substances at 60°C. for one hour.

All of the juices, commercial extracts and preparations as well as the medium and other control solutions were tested for lipase content by the method described by Willstätter, Waldschmidt-Leitz and Memmen (1923). None of the substances showed the slightest lipolytic activity when tested by this method.

The titre of the complement content of the fresh tissue juices varied between one to two and a titre of one to thirty-two. This was excellent proof of the freshness of the juices. Heated juices, commercial tissue extracts, solutions of powdered tissue and tissue secretions exhibited no complement content. Tissue juice prepared from the organs which contained the least amount of blood naturally showed the lowest complement content.

Qualitative complement fixation tests were run on the tissue juices and control solutions. Two antigens were used: one, the fresh bacillary suspension, and the other, a standard Parke-Davis preparation. None of the solutions tested showed any antibodies against the tubercle bacillus antigen when tested by this method.

Tissue juices and control solutions were tested for lysozyme content against a microörganism isolated from the air which seemed to dissociate readily and to be lysed easily by lysozyme prepared from nasal washings. The tissue juices were not treated in any way, but were used in their fresh state or after heating. Undiluted serum, whole blood, and those juices from organs containing large amounts of blood seemed to show

a slight lytic action on the air coccus. No evidence of lysozyme action was noted in the other preparations.

Hydrogen-ion determinations were performed on all the solutions at the time of preparation. These determinations were checked after the solutions had been added to the medium.

## RESULTS

The experiments with blood were carried out with whole blood, serum, heated serum, plasma and heated plasma. After the three-week period of growth on medium containing whole blood, the microörganisms had developed moderately well and showed no morphological changes. The hydrogen-ion concentration of the mixtures increased from pH 7.2 to about pH 6.0. After that period the microörganisms rapidly attained maximum development and the hydrogen-ion concentration increased to approximately pH 5.0. Apparently whole blood had little effect in low concentrations on the tubercle bacillus.

In the cultures containing twenty per cent of whole blood, however, marked inhibition was observed. This particular experiment was then repeated twice in duplicate. In every case, twenty per cent whole blood or a larger quantity of whole blood showed a definite inhibitory action on the growth of the microörganism.

The effect of serum and of plasma was approximately the same. These substances showed a marked retarding effect on the growth of the tubercle bacillus. Growth was very slow in starting on medium containing serum or plasma. Ultimately there seemed to be no real inhibition of growth, for after a period of six weeks the cultures finally attained satisfactory development. However, during the early period of growth, the hydrogen-ion concentration did not increase at first and then increased very slowly, another indication that growth was retarded, if not inhibited. The higher the concentration of serum or plasma the greater the retardation. In no way did the microörganism seem to have been affected by its exposure to serum or plasma. The bacilli did not grow at all on pure serum. Subcultures in control medium showed that the bacilli had not been destroyed by the serum. It was definitely an inhibition phenomenon. The experiments which were performed with heated serum and heated plasma were, as far as could be determined, almost identical with the unheated substances in the higher concentrations. The microörganism did not grow on the undiluted heated serum or heated plasma, although subcultures showed that there

was no killing; ten and twenty per cent of heated substance showed some retarding action. In the lower concentrations, however, there was, contrary to the previous experiment, no inhibition, and no retarding of growth. In every case, the controls attained a four-plus normal growth.

Brain substance was particularly difficult to investigate. In the first place, it was very hard to filter, and in the second place, it became easily contaminated. The hydrogen-ion concentration in the beginning of the experiment was pH 6.5 and never dropped below pH 6.0. Growth on brain substance and on heated brain substance showed marked inhibition. The cultures never attained more than a one-plus growth. Slight increase in hydrogen-ion concentration was probably due to the fact that growth was almost entirely inhibited by the brain substance. It is interesting to note that such marked inhibition of growth took place without deleterious effect on the microörganism.

The experiments with the thyroid gland were carried out in several ways. Thyroid tissue juice was used, both heated and unheated, a commercial preparation of thyroxin in liquid form and dessicated thyroid in powder form were tested. The latter was used in a one to five dilution in sterile distilled water.

All of the solutions had a marked effect on the growth of the tubercle bacillus. The juice prepared from fresh gland hindered the development of the microörganisms to such an extent that only a one-plus growth was obtained after six weeks' incubation in medium containing small amounts of juice. No growth was obtained in the bottles containing higher concentrations of thyroid juice. There was no demonstrable difference between the effect of heated and unheated thyroid juice. There was absolutely no growth with dessicated thyroid and with thyroxin, regardless of the concentration. The microörganism was not able to develop at all on the undiluted substance of any of the four kinds used.

It is interesting to note two facts. The hydrogen-ion concentration increased from pH 6.0 (highest) to pH 5.5 at its lowest reading. This is remarkably little activity for cultures of tubercle bacilli.

Tissue juice prepared from heart muscle was tested in heated and unheated states. There was apparently no difference in results. The heart tissue juice exerted a very marked inhibitory effect on the growth of the bacilli. After six weeks, a one-plus growth was obtained in most of the cultures. The hydrogen-ion concentration had increased

from pH 6.8 only as far as pH 6.0. There seemed to be no difference in the cultures containing two per cent tissue juice or twenty per cent tissue juice. Apparently the action was just as great with smaller concentration. This result did not seem to be in accordance with experiments on other tissue juices and therefore the entire series of experiments was repeated in duplicate; the same results were obtained.

The effect of the juice prepared from lung tissue upon tubercle bacilli was one of the first to be investigated. As might be expected, it gave very satisfactory results, although the tissue juice contained large amounts of blood, and although very small amounts of juice were obtainable from whole lungs.

There seemed to be an absolute lack of any inhibiting, retarding, lysing, or bactericidal substance for tubercle bacilli in the tissue juice prepared from lung, heated or unheated. On the contrary, lung tissue juice seemed to enhance the growth of tubercle bacilli.

The lung tissue juice was so effective in increasing the growth of tubercle bacilli that it was difficult to differentiate between the effect of small amounts and of large amounts. At the end of three weeks, the cultures containing two per cent lung tissue juice showed as great, if not greater, development than did the control cultures. The hydrogen-ion concentration of the cultures increased from pH 6.8 to pH 4.5, the lowest pH value obtained in any set of cultures, and far lower than that obtained in any other experiment. This indicates the tremendous activity, the enormous rate of growth of the microörganisms when subjected to this substance. (Were this tissue juice less difficult to prepare in quantity, it might be of use in obtaining early, luxuriant, diagnostic cultures of tubercle bacilli.)

Most of the cultures containing lung juice, developed a maximum growth in about eighteen days. In these cultures there seemed to be no change in morphology or staining characteristics of the microörganisms. They were not stained more brilliantly and did not appear larger; there was no increase in virulence. Apparently lung tissue possesses a substance which simply enhances the development of tubercle bacilli. This may be a factor in the high incidence of pulmonary tuberculous infection.

Several solutions were tested in the experimental investigation of the effect of the pancreas on tubercle bacilli. These consisted of heated and unheated pancreas juice, commercial pancreatic digests prepared by dissolving one per cent of a powdered pancreas dispert in 0.125 per

cent sodium carbonate solution. In addition to the usual controls, broth cultures of tubercle bacilli were made after the broth had been titrated to a hydrogen-ion concentration of approximately pH 4.5 in order to control the low hydrogen-ion concentration of the insulin, which is contained in acid solution.

Both pancreatin and pancreatic digest apparently had no effect on tubercle bacilli.

Heated and unheated pancreas juice showed a marked inhibiting effect on the growth of the tubercle bacilli. This increased with the concentration of the tissue juice and no growth was obtained on undiluted juice. This phenomenon seemed to be true inhibition without any evidence of lytic action and without any change in the biological characteristics of the microörganisms at all.

Sodium carbonate had no effect on the microörganism at all. In the experiments with insulin, it is interesting to note that the high acid content of the controls did not inhibit the development of the microörganism. The tubercle bacilli began to grow somewhat more slowly on the very highly acid medium, but the final hydrogen-ion concentration of the cultures was not much higher than at the beginning of the experiments.

In the first experiment with insulin, the cultures immediately attained a four-plus growth even in the bottles containing large amounts of that solution. This did not seem reasonable and therefore the experiment was repeated several times. The insulin showed no effect on tubercle bacilli in two of the three repeat experiments; the findings were the same as in the previous experiments. There was complete inhibition in the third experiment, but when this was repeated for a fourth time, there was again no evidence of any effect of insulin on the growth of tubercle bacilli. A source of error such as improper seeding of the bacilli or overheating of the culture bottles probably accounted for these experimental results which differed from the others. It may be concluded that commercial insulin has no inhibiting or retarding effect on tubercle bacilli; there is certainly no enhancing effect, and probably no effect of any kind.

There seems to be a certain indefinable opinion on the part of investigators that nucleic acid is a substance which tubercle bacilli very easily assimilate, and which may be used as an excellent source of food for that microörganism.

The tubercle bacilli were apparently unable to utilize nucleic acid.

The substance showed a marked inhibiting effect on the development of the tubercle bacillus. There was no development of tubercle bacilli on the medium containing nucleic acid, with the exception of the cultures containing the smallest amounts, 2 per cent and 4 per cent nucleic acid. The hydrogen-ion concentration was near pH 4.0 at the start and did not increase measurably during the experiment.

The tissue juice prepared from liver exerted a moderate amount of inhibition on the growth of the tubercle bacilli. None of the cultures developed to a maximum growth; the readings ranged between a two-plus or three-plus growth after prolonged periods of incubation. No definite growth developed in many of the cultures, especially in those containing large percentages of liver juice, but a slight film of "plus-minus" degree containing stainable bacilli showed that some slight growth activity had taken place. The hydrogen-ion concentration of the cultures also contributed to this conclusion. This increased from pH of 7.0 to pH of 6.2 at the end of the experiments. No change in morphology or staining characteristics of the microörganisms could be noted even in the faint films which developed on some of the cultures. The usual non-acid-fast forms found in very young cultures of tubercle bacilli could be demonstrated. This was a phenomenon of age and not of the action of the test fluid.

The preparation of tissue juice from the spleen was very difficult due to the large amount of fibrous material. The effect of this fluid on tubercle bacilli seemed to compare quite favorably with the liver juice. The inhibition was definite. Its true inhibitory action was marked when contrasted with the retardation observed with other fluids. The tubercle bacilli did not develop well and never attained a maximum growth. The biological characteristics of the bacilli were unaffected by the marked inhibition. The hydrogen-ion concentration of the cultures increased from approximately pH 6.4 to approximately pH 6.0, a range which shows the small amount of activity.

This inhibition of the growth of tubercle bacilli by spleen tissue juice may possibly account for some of the observed therapeutic success. It is probably not the only reason since the same therapeutic results are not obtained with other tissues.

The preparation of tissue juice from the kidney was accomplished with comparative ease. The hydrogen-ion concentration of the cultures in the beginning of the experiments was pH 6.4 and this later increased to pH 5.8. The kidney exhibited almost complete inhibition of the

growth of tubercle bacillus in one experiment and in another inhibition. In the first series, the cultures containing the smallest amount of kidney juice, that is, 2 per cent, attained a growth graded at two-plus. These were the only cultures which showed any growth at all. In the other series of experiments absolutely no growth was observed. In a third series of experiments, very slight amounts of growth were noted and it was from this series that the hydrogen-ion concentration determinations were made. In other words, the effect of the kidney tissue juice on the tubercle bacilli was definitely one of inhibition showing, as did the other substances tested, no evidence of lytic or bactericidal properties.

TABLE 1

*Correlation of the effect of various tissue juices on tubercle bacillus with incidence of tuberculosis of certain organs*

| TISSUE FROM WHICH JUICE WAS PREPARED IN ORDER OF GREATEST SUSCEPTIBILITY TO TUBERCULOSIS AS EVIDENCED BY CLINICAL STATISTICS | pH OF TISSUE JUICE WHEN PREPARED | pH OF BROTH CULTURES PLUS TISSUE JUICE AT | | ACTION OF TISSUE JUICE ON GROWTH OF TUBERCLE BACILLI |
|---|---|---|---|---|
| | | Beginning of experiments | End of experiments | |
| Lungs | 6.8 | 6.8 | 4.5 | No retarding effect |
| Blood | 7.4 | 7.2 | 5.0 | No marked effect |
| Liver | 7.0 | 7.0 | 6.2 | Moderate inhibition |
| Spleen | 6.9 | 6.9 | 6.0 | Moderate inhibition |
| Kidney | 6.0 | 6.4 | 5.8 | Marked inhibition |
| Brain | 6.5 | 6.7 | 6.2 | Marked inhibition |
| Pancreas | 6.6 | 6.8 | 6.0 | Marked inhibition |
| Thyroid | 6.5 | 6.8 | 6.2 | Marked inhibition |
| Heart | 6.8 | 6.8 | 6.0 | Marked inhibition |
| Controls | | 7.0 | 4.5 | Maximum growth |

The degree of increase in hydrogen-ion concentration indicates the degree of development of growth.

Subcultures were made from test cultures to control medium. Those test cultures which showed no growth were centrifuged and subcultures made from the sediment.

There was no demonstrable change in morphology, characteristics of growth, or virulence of the organism after subjection to the tissue juices.

## DISCUSSION

Certain factors in the development of the tubercle bacillus have been eliminated. Complement, associated by many investigators with the phenomenon of resistance to disease, was shown to be present in normal

amounts in the tissue juice preparations, and varied, as one would expect, with the amount of blood in the organ under consideration. Tuberculosis antibodies, commonly associated with the resistance produced in response to first infection in tuberculosis, were shown to be absent in any measurable amounts in the tissue juices under investigation. The free oxygen and carbon dioxide supply of the tissue juices was approximately the same for all, while oxygen and carbon dioxide in combination were probably present to a somewhat lesser degree than they were found in the tissue *in vivo*. This was probably due to the mechanical preparation of the tissue juices. In every other way, the tissue juices approximated as nearly as was possible the chemical constitution and fresh state of living tissue itself.

These experiments substantiate the investigations of Pinner (1937), Corper (1932) and others who showed that lysozyme is potent only against nonpathogenic microörganisms and has no effect on the tubercle bacillus.

It therefore seems possible to eliminate entirely the question of food, blood, antibodies, complement, gases and lysozyme in the tissue juices as factors which could explain the results of the experiments reported here. Nor can organ specificity in tuberculosis be credited to any of these factors.

It might well be expected from the reports in the literature on the effect of various body fluids and tissues on tubercle bacilli, and from the clinical evidence of resistance in certain organs, that the tissue juices should show some inhibitory action on the growth of the tubercle bacillus. In other words, it is certain that the kidney tissue itself exerts an inhibitory effect on the growth of tubercle bacilli, whether or not the resistance of the kidney is due to the copious blood supply and large blood vessels of that organ. The same can be said for other tissues.

If one considers all of the evidence presented by previous investigators, one cannot fail to be impressed by the fact that the one single opinion most frequently stated describes bactericidal and bacteriolytic effect of tissue on tubercle bacilli. One of the reasons for this is unquestionably the fact that Porter's work (1917) has been generally accepted by most investigators and printed over and over again without question in the textbooks.

The experiments reported here show absolutely no evidence of a bactericidal or bacteriolytic element in tissue juice. Certain investigators have assumed the active principle to be bactericidal or bacteri-

olytic without experimental proof while others have stated the absence of proof and still described "digestive" activity.

The inhibiting and retarding effect of the tissue juices may have killed a few of the microörganisms, but, as Long (1930) stated, "evidence of previous death," lysis, change in morphology and staining characteristics of the microörganisms was lacking. It seems justifiable therefore to conclude that the action of certain tissue juices was purely inhibitory to a greater or lesser degree. The degree of inhibition of tissue juice prepared from certain organs seems to compare directly with the resistance of that tissue to tuberculous infection as evidenced by clinical investigation.

The possible reason for this inhibitory action, possessed by certain tissues and not be others, seems to be due to some element which is not demonstrable by ordinary means. It probably is tied up in some way with the natural immunity, or resistance of the tissues, since it is found in fresh, normal tissue. This element is possibly not specific for tubercle bacilli, but may be a nonspecific factor such as the growth-stimulating substances found in certain tissues by other investigators. Whatever the substance may be, its action is definite, measurable and potent.

## CONCLUSIONS

1. Tissue juices prepared from certain fresh normal human organs exert an inhibitory action on the growth of the human tubercle bacillus.

2. The effect of the tissue juices is definitely one of inhibition. The degree or extent of inhibition varies in different organs. The growth inhibiting factors were, however, relatively constant for each organ examined.

3. There is no evidence of bactericidal or bacteriolytic action.

4. The degree of inhibition exerted by various tissue juices on the tubercle bacillus seems to compare directly with the resistance of the organs to tuberculosis as evidenced by the clinical incidence of the disease.

5. Evidence has been presented to show that the inhibitory element in the tissue juices is not a lypase, nor lysozyme, and is not associated with antibody content, complement, food or blood supply of the tissues investigated.

6. The nature of the inhibitory element in tissue juices prepared from certain organs is not known. It may be a specific or a nonspecific factor. It can be best considered at this time to be nonspecific.

## BIBLIOGRAPHY

(1) BRINES, O. A.: An analysis of 1,535 autopsies, Amer. J. Clin. Path., 1932, *2*, 37.
(2) CAMERON, C.: Point of entry in tuberculous infection, Lancet, 1934, *227*, 1275.
(3) CORPER, H. J.: Lysozyme and tuberculosis, Amer. Rev. Tuberc., 1932, *25*, 59.
(4) ERBA, B.: Esiste una battericidia specifica nella tubercolosi, Biochem. e. terap. sper., 1933, *20*, 22.
(5) KRAUSE, A. K.: Environmental factors in tuberculosis, Amer. Rev. Tuberc., 1920, *4*, 713.
(6) LONG, E. R.: A chemical view of the pathogenesis of tuberculosis, Ibid., 1930, *22*, 467.
(7) MILLER, J. A.: The evolution of pulmonary tuberculosis, Ibid., 1936, *34*, 301.
(8) NOLAN, L. E.: A statistical study of 1,250 autopsies in Veterans' Administration Hospitals, Med. Bull. Vet. Admin., 1932, *9*, 124.
(9) PINNER, M., AND VOLDRICH, M.: Lysozyme, the occurrence of an apparently sterile phase: The relation of lysis to dissociation, Jour. Infect. Dis., 1937, *60*, 6.
(10) PORTER, A. E.: Bacteriologic action of gland extracts on tubercle bacilli, Jour. Hyg., 1917, *16*, 55.
(11) REISS, P., AND SIMONIN, C.: Les variations post-mortem des tissues, Compt. rend. Soc. de biol., 1937, *97*, 306.
(12) ROSENOW, E. C.: The newer bacteriology of various infections as determined by special methods, Jour. Amer. Med. Assn., 1914, *63*, 903.
(13) SEEGAL, B. C., AND KHORAZO, D.: A method of obtaining undiluted tissue juice for the study of tissue antibody titer, Proc. Soc. Exp. Biol. & Med., 1934, *31*, 435.
(14) SEIBERT, F. B.: The isolation and properties of the Purified Protein Derivative of tuberculin, Amer. Rev. Tuberc., 1934, *30*, 713.
(15) TUNNICLIFF, R., HOWELL, K. M., AND HIRSCHBERG, N.: Complement fixation and opsonification tests of smooth and rough tubercle bacilli with the serum of patients suffering from different grades of tuberculosis, Jour. Infect. Dis., 1935, *56*, 111.
(16) WILLSTÄTTER, R., WALDSCHMIDT-LEITZ, E., AND MEMMEN, F.: Bestimmung der pankreatischen Fettspaltung, Zeitr. f. Physio-Chemie., 1923, *135*, 93.
(17) WILSON, G. S.: Tuberculous bacillaemia, Med. Res. Counc. Spec. Rep. Ser., 182, His Majesty's Stationery Office, London, 1933.

# TUBERCULOSIS CONTROL[1]

## Present Deficiencies—Future Requirements

ROBERT E. PLUNKETT

There is definite evidence that a renaissance in the field of tuberculosis control is imperative if mortality and morbidity from this disease are to be further reduced. Forces making for the control and for the spread of the disease appear to be stalemated. Most needed to promote future progress are the dynamic forces which characterized the campaigns of the first and second decades of the present century. In spite of scientific advances in case-finding and methods of treatment, administrative programs of tuberculosis control in many localities have become static.

The responsibility for the shortcomings of the present administrative services and for the inadequate number and type of hospital beds for tuberculosis rests with both the unofficial and official agencies. Although the official or governmental agencies may carry on accepted administrative services, they must, by the very nature of their employment, rely on the unofficial for active, vigorous leadership in the promotion of any new service, hospital or otherwise, which involves large appropriations or a major change in policy.

Too many physicians and others engaged in tuberculosis work appear to be willing to rest upon the laurels won in the splendid program developments of twenty or thirty years ago. Some who participated in those early promotion campaigns seem to have lost their vigor and enthusiasm. Newcomers to the crusaders' ranks soon have become lulled into a false sense of security.

This apparent indifference regarding tuberculosis is reflected by the man on the street who feels, in the absence of a case of tuberculosis in his family or friends, that the tuberculosis problem is solved.

The public is not aware of the magnitude of our present tuberculosis problem. To be sure, the death rate has dropped from 201.9 in 1900 to 55.0 per 100,000 in 1935 in the United States. This disease still is the leading cause of death among persons between the ages of 20 and

[1] From the New York State Department of Health, Division of Tuberculosis, Albany, New York.

39. Recent figures published by the Metropolitan Life Insurance Company reveal that, of forty states reporting for 1936, nineteen recorded a tuberculosis mortality higher than in 1935, and nineteen lower, while two states experienced no change in mortality. Even though we do not experience a rise in the tuberculosis death rate, we do not appear to be justified in anticipating during the next two or three decades a decline comparable with the percentage decline in the past twenty-five years. The high death rate among the older age groups is extremely significant, for elderly consumptives can and do spread tubercle bacilli.

If continuity of expression is essential to successful advertising, then we should provide an active, continuous program of public health education regarding tuberculosis throughout the entire year.

In spite of our increased knowledge of bacteriology, epidemiology, prevention and treatment, many physicians engaged in tuberculosis work think and act only in terms relating to the topographical location and extent of a pulmonary lesion. To be sure, the precise definition of the character and extent of a lesion is important, but equally, if not more important, are the epidemiological factors involved. It is the evaluation or appraisal of these latter factors which is necessary if prevention and control measures are to be effective.

One of the reasons for this lack of appreciation of the control factors may be gleaned from a review of the influences which have motivated those engaged in tuberculosis work. The development of the tuberculosis program may be divided into three eras.

The first one was largely characterized by a humane motive to offer some assistance in providing better care for the enormous number of poor consumptives. Funds were raised by private subscriptions for the maintenance of dispensaries, clinics and, occasionally, hospitals. Physicians also gave of their time and services gratuitously.

It soon became apparent that tuberculosis was, to some extent, a public responsibility, and appropriations were made in various sections of the country for tuberculosis sanatoria or hospitals. This opened up the second era. The laboratory and X-ray came into prominence. Improved diagnostic technique and sanatorium observation made it possible to define more accurately the extent and behavior of a pulmonary lesion; a new specialty was born, and a new specialist who usually could be identified by his white coat with a stethoscope hanging as a lavaliere from his neck. His interest was primarily concerned with a sick person having pulmonary tuberculosis and he was little concerned with any-

thing above the larynx or below the diaphragm and much less with the epidemiological aspects of the disease.

Recently, we have entered the third era in which, in addition to providing for the individual patient, we are beginning to talk and act with relation to the public health and economic significance of tuberculosis. The tremendous and devastating economic influence of tuberculosis upon society is being recognized. We are thus abreast of the position taken by Chadwick in 1842 in his *General Report on the Sanitary Condition of the Labouring Population of Great Britain* when he urged economic self-interest as an argument in favoring sanitary reform.

It should readily be apparent from a review of the death rates by occupation, as well as by age and sex, that the large numbers of tuberculosis patients who are found among the underprivileged and low salaried groups create an economic burden, the great weight of which may be realized when the cost of protracted hospitalization is taken into consideration. Society is paying this big tuberculosis bill whether it realizes it or not.

In order, therefore, to effect future human and financial economy, the time has arrived for us to make a critical appraisal of the present tuberculosis problem and its possible future significance. Equally important is the need for a qualitative, as well as a quantitative, inventory of the existing facilities to meet the problem.

The size of the present tuberculosis problem can with reasonable accuracy be determined by the mortality figures plus an estimate of the number of cases in relation to the deaths. Although estimates of the number of cases per death reported by different observers vary, the experience of the New York State Department of Health in rural New York indicates that there are about six active cases and between two and three inactive, recovered or border-line cases per death. All these cases should receive some service from the tuberculosis hospital or clinic.

Therefore, in the United States there are approximately 500,000 cases of tuberculosis which need intimate, close follow-up or hospital treatment.

As regards the future trend of the tuberculosis rate, I feel that we know altogether too little about the many biological and environmental influences which are playing a part in the behavior of this disease to warrant the statement that it can be eradicated. However, if we can put into execution a program by which the known methods of preven-

tion and treatment can generously be applied, then we may look expectantly to the day when the word "control" will connote something real, and the public health and economic burden resulting from the disease will be materially reduced.

Special consideration should be given to the most costly yet most important feature of the tuberculosis program—the tuberculosis hospital. That the tuberculosis hospital has contributed to the decline in tuberculosis cannot be denied. This contribution, however, can mostly be attributed to the segregation of thousands of sources of infection rather than to cures. The tuberculosis hospital or sanatorium could not justify the expenditure over the past years of millions of dollars on the basis of returns to society in the form of recovered or cured cases.

The conditions or circumstances which prompted this statement should be looked upon as a challenge by every person engaged in or concerned with the furtherance of protective public health facilities.

The modern tuberculosis hospital and the well equipped, well conducted case-finding and follow-up clinic are society's most valuable administrative weapons against this disease. They are more formidable still when combined into one service.

The epidemiology of tuberculosis being a study of the disease as a mass phenomenon, the most important administrative procedure is case-finding. For convenience, this service may be grouped under two general headings, the local clinic or dispensary and the X-raying of special population groups.

Unfortunately, there are no detailed data readily available regarding the number and nature of services being rendered in the clinics throughout the United States.

The chest clinic, when properly and scientifically equipped and conducted, cannot only produce a profitable yield in new cases, but through the local physicians and public health nurses it is possible to extend its educational and prophylactic benefits into the homes. The participation of the practicing physicians is extremely valuable to a chest clinic program. The New York State Department of Health has, by virtue of the sympathetic cooperation of the practicing physicians, been able to produce by the examination of contacts of known cases, plus patients referred by private physicians, a larger yield in new cases than by any other method, except possibly the X-raying of selected groups of persons found in racial or other groups in which the death rate is particularly high.

I am confident that an objective appraisal of the 1,000 local clinics and dispensaries throughout the country is not only needed but would reveal a very disheartening picture. Most clinic administrators lack appreciation of the value of complete socio-epidemiological and clinical data. Too many clinics are conducted merely as a place where a patient may be examined, and lack the broad approach to the tuberculosis problem which is essential if control is to be realized.

The case-finding studies reported in the literature show a percentage yield of positive cases from .01 per cent up to approximately 5 per cent. When the age distribution of the persons examined in these special case-finding studies is reviewed, it becomes further apparent that there is a need for emphasis on case-finding in the late adolescent and adult groups, especially among the underprivileged. Moreover, a more intimate consideration of the problem of tuberculosis among certain industrial groups is warranted. A study which we are now conducting of patients in general hospitals shows that a relatively large number of persons treated in general hospitals for nontuberculous conditions may be found to have pulmonary tuberculosis.

We are, however, greatly indebted to the American Medical Association for its splendid survey of tuberculosis hospitals and sanatoria made by Dr. Fritjof H. Arestad from data of the years 1933–1934.

This survey reveals that there are in the United States 1,240 institutions containing 95,198 beds for the treatment of tuberculosis. At the time the survey was completed, plans were under way for 6,661 additional beds. Let us, for the purpose of discussion, say that there are now 100,000 beds available for the treatment of tuberculosis. The annual average number of tuberculosis deaths in the United States for the three-year period, 1934–36, was 71,071, or a ratio of 1.4 beds per death. In determining a desirable bed-death ratio, consideration of how these beds are used needs emphasis. There were slightly over 7,000 children under treatment on the date when the census was taken and presumably the majority of these were of the so-called childhood type of tuberculosis. Although the use of these beds in hospitalizing children may contribute indirectly to the preventive program, only hospital or sanatorium beds in which pulmonary tuberculosis of the so-called adult type is treated should be counted. At the same time, about 4,000 beds were in tuberculosis hospitals each of which had a capacity of less than 50. This represents a total of at least 11,000 which should be given qualitative consideration before determining the minimum number of beds which may be required to meet the acceptable standard of two beds per death. That many states have a smaller

number of beds than even the minimum requirement is evidenced by the fact that sixteen states have less than one bed per death and twenty-one states with between 1 and 1.9 beds per death. Only twelve states have two or more beds per death. Although in certain metropolitan sections three beds per death seem to be required, it may be that in view of the declining death rate and the scientific advances in diagnosis and treatment, two beds per death could be used effectively for many years to come. Unless the chemists or biologists or bacteriologists discover some substance which will bring the disease under control more rapidly, it is not likely that the drop in the death rate will be as rapid during the next two or three decades as during the past quarter of a century. It appears, therefore, that at least 50,000 additional beds will be necessary to meet the standard of two beds per death.

According to the survey, the replacement value of the hospitals surveyed was estimated to be about $329,000,000, while the annual cost of administering the hospitals was $75,000,000. With special reference both to the investment and maintenance cost, it should be emphasized that the construction cost included all sorts of sanatorium type buildings constructed during the past thirty years. Among these are many institutions which are only slightly superior in construction characteristics to the traditional 'lean-to'. On the other hand, the estimate includes many modern tuberculosis hospitals.

It is unusual to find a tuberculosis sanatorium of less than fifty beds which can afford to provide professional equipment and service to meet the needs of modern medicine. This being so, is it not evident that about 28 per cent of the sanatoria may be outmoded? In addition, another 28 per cent have a capacity of between 50 and 100 beds. Although many sanatoria in this group may be providing creditable service, it is questionable whether it would not be better economy to have fewer and larger sanatoria, except where the mortality figures indicate that 100 beds or less may adequately fill the need.

Recently, the New York State Department of Health conducted an intimate survey of a group of small county tuberculosis hospitals, each of which had less than fifty patients. The survey revealed no facts which, by any stretch of the imagination, would indicate that these institutions were other than custodial in character. There was little semblance of a program of scientific diagnosis and treatment. Each of the hospitals was a definite fire hazard, and the census at the time of the survey showed that there were housed in each of them many persons who showed no evidence of tuberculosis. If this same condition prevails throughout the country, we do not need further evidence of the need of closing such institutions.

It should be noted, however, that of the 28 per cent of the tuberculosis

hospitals having less than fifty beds, the total number of beds in such hospitals conducted as public tuberculosis hospitals was 1,972. In addition, there are 1,993 beds in private tuberculosis hospitals having a capacity of less than fifty beds. Of the 28 per cent of the hospitals having a capacity of between fifty and ninety-nine, those operated as public tuberculosis hospitals have 5,176 and those as private hospitals or sanatoria have 3,714 beds.

That further improvement is necessary, in many tuberculosis hospitals, in the technical equipment and service may be gleaned from the following:

Of the 471 sanatoria throughout the United States, 406 have facilities for artificial pneumothorax treatment, 364 for minor surgery, and 152 for special chest surgery. X-ray equipment is available in only 364, or 77 per cent of the sanatoria. While 364 sanatoria have clinical laboratory facilities, only 124 have facilities for necropsy work.

The survey indicates that in approximately one-fifth of the sanatoria, the clinical and statistical records are inadequate and, in many instances, entirely lacking. It is rather difficult to visualize a progressive medical and surgical program in the absence of a well rounded clinical and pathological laboratory service. To be sure, many institutions mentioned in the survey refer their laboratory work outside. This system may, in some instances, provide satisfactory service. The clinical laboratory, except in the very small tuberculosis sanatoria or hospitals, many times serves as a guide both in the diagnosis and the treatment of the disease. From the report of the percentage of necropsies obtained, it appears that if the splendid educational material available in the tuberculosis institutions is to be used profitably, more interest in post-mortem examinations is necessary. While the city tuberculosis institutions secure necropsies for 37 per cent of their patients, and the federal 25 per cent, all of the other subdivisions vary between 9 and 15 per cent.

By the same token, the large number of sanatoria reported in this survey in which complete clinical and X-ray laboratories, and provisions for pneumothorax treatments are lacking, either in part or entirely, leaves much to be desired. On the other hand, it is assumed that the tuberculosis departments in general hospitals have the benefit of the other services prevailing in most general hospitals.

It must be admitted that the vast amount of clinical material available in tuberculosis hospitals is not being used as much for teaching as it should be. Sixty-three tuberculosis hospitals and 159 other hospitals admitting tuberculous patients provide training for interns. Eighteen sanatoria have established

schools for nurses and thirty-one have reported courses of affiliation. Of the 740 general hospitals with tuberculosis departments, only 268 conduct nursing schools. Obviously, the tuberculosis hospital program is not taking advantage of the available material and opportunities in contributing to professional advancement in our knowledge of tuberculosis by affiliation with schools of nursing.

The qualitative aspect of the service rendered in tuberculosis institutions is fundamentally as important as the quantitative. To some degree, facilities for the care of tuberculosis cases tend by nature to become static, whereas the scientific needs are dynamic and change constantly. The application of modern methods of study, diagnosis, and treatment demands more from the standpoint of scientific equipment, nursing and medical personnel, than formerly. The treatment of tuberculosis has been transformed from a policy of passive expectancy to one of active patient assistance.

In what manner tuberculosis beds are being used, in relation both to treatment and to segregation, is important. Of the pulmonary cases reported in this survey, only 13 per cent were admitted in the minimal stage of the disease. Thus, more than 80 per cent of tuberculosis cases do not have the benefit of hospital treatment sufficiently early in the disease to expect reasonably prompt recovery. As a matter of fact, only about 20 per cent of the discharged cases are either arrested or apparently arrested, about 24 per cent are deaths and the 47 per cent who are discharged as improved or unimproved presumably return home in the communicable stage of the disease. These, in addition to the more than 80 per cent who were spreading tubercle bacilli before admission, create a major public health problem.

Of all the deaths from tuberculosis, only 22 per cent occur in tuberculosis hospitals. In contrast to this, in upstate New York 45.8 per cent of all tuberculosis deaths occur in public and private tuberculosis hospitals, 31.8 per cent in the home, and 11.6 per cent in general hospitals with no separate provision for tuberculosis cases. These facts indicate that more advanced and terminal cases should be properly segregated.

It is obvious that there is urgent need for more progressive case-finding and case-holding programs. In upstate New York, the responsibility for case finding rests with health departments and particularly with county and State tuberculosis hospitals. In conjunction with the health departments, clinics for contacts, suspects, and others are conducted throughout the State. Case finding should be recognized more generally as the responsibility of public tuberculosis hospitals. Their staff members are experts in diagnosis. Such a system provides a continuity of service for patients from discovery through treatment, and these physicians being on full-time duty, as they should be, are not commonly looked upon as competitors in general practice.

This survey gives proof from the status of discharged patients that few, if

any, institutions are 'case-holding', as they should be. The grave danger that lies in discharging a patient whose recovery has not reached a point which may assure him of relatively good health and possibly a return to economic self-sufficiency needs emphasis. It is a waste of public funds to treat a patient for a few weeks or months and then turn him loose, knowing that he is doomed either to readmission in hopeless condition or to death. Of greater significance is the discharge of so many patients, whose sputum is positive, back into the community further to spread infection. Important as this may be to the individual patient, the seriousness to the family and the community of releasing patients whose sputum may be potentially or actually positive, needs more general recognition. A situation which permits such a large number of patients whose disease is in the infectious stage to be sent back into their homes is a grave one. Every person concerned with tuberculosis control, including clinicians, can well afford to give this problem painstaking thought and study. Find out the reasons why patients go home; if they can be defined, then remedial measures can be found. Hospital administrators must broaden their viewpoints to that of family and community responsibility if they hope to fulfill their obligation to society.

Granting that early diagnosis, followed by prompt, scientific treatment, is a prime factor in furthering the control of the disease, probably our next most important problem is to enlarge upon our efforts to return a greater number of patients back to their communities on a sound economic basis. Such a hope can never be realized until more and better facilities for education, training, and rehabilitation assume a conspicuous place in the tuberculosis program of every state.

The education of the patient should start the moment he is told he has tuberculosis, it should continue throughout his hospital or sanatorium residency, and be followed by only less intensive post-sanatorium advice and guidance. Although we do not all have the happy faculty of telling patients they have tuberculosis and making them glad of it, much can be done to have the patient assume a sensible attitude before hospitalization.

The adjustment of each patient to his new environment and the solution of endless family, industrial and economic problems are of paramount importance if optimum results from treatment are to be realized. More than casual or intermittent contact with the physician is needed to create the proper attitude toward "the cure." This implies a personal physician association which is most commonly found in sanatoria having full-time staffs.

Adult training and education of tuberculosis patients should be provided in most tuberculosis hospitals. In cultivating avocational as well as vocational interests, the cure of the patient has been well begun.

The consequent substitution of a broader and more encouraging outlook on life and on the world in general during the prolonged period of mental idleness and worry over his disease plays an important part in "the cure." It is absurd in most cases to advise a patient upon discharge to go and get a light outdoor job. Light outdoor jobs just are not to be found. It is good social as well as medical economy to take time to equip patients mentally as well as physically to return to their communities prepared to be self-sustaining.

Excluding schools for children, only forty-five sanatoria conduct schools for adults and fifty-three have industrial rehabilitation courses. The psychological advantage of a planned future during the program of cure is extremely valuable. Although hope springs eternal in the mind of the tuberculosis patient, tangible evidence of the possibility of returning to society on a self-sustaining basis such as may be found in an educational, academic, or vocational training, pays real dividends.

The fact that the disease of 60 per cent of discharged patients is unstabilized with the resultant positive sputum in most cases is a real challenge. Rather than needing so called after care, the majority of these patients need continued hospital care. If this situation can be met, it should markedly reduce the size of our after-care problem.

There is in the United States a deplorable lack of opportunity for recovered cases of tuberculosis to complete adequately their rehabilitation or to find proper employment in an environment that will give reasonable guarantee of their continued economic security. From the administrative as well as the economic standpoint, the after-care and rehabilitation program, so woefully lacking at the moment, should be made universally available and be integrated and administered as one service to provide greater opportunity for:

(*1*) An extension of therapeutic assistance
(*2*) Continued segregation of positive sputum cases
(*3*) More thorough conservation of the benefits of past treatment
(*4*) Improvement in the socio-economic status of both the patients and their families

In the absence of such a service, optimum returns for the money spent on hospitalization can never be realized, and many potential tax producers will be continued as tax consumers and as menaces to public health.

In *summarizing*, the following major items deserve emphasis:

1. There is need for at least 50,000 additional beds. Ill-founded optimism regarding the decline of tuberculosis has led too many people into a sense of false security. Tuberculosis still takes its greatest toll in the age group when men and women are society's greatest asset. Tuberculosis hospital beds are essential for segregation, treatment and recovery. Each state should have a minimum of two beds per death. It is my impression that, if it should be impossible to have furnished satisfactory construction and adequate medical and epidemiological service for the above number of beds, fewer hospital beds proportionately distributed on the basis of the geographic distribution of morbidity and mortality would be more desirable.

2. The location and distribution, geographically, of tuberculosis hospital beds in each state should be determined only after critical analysis of the disease problem and qualitative as well as quantitative study of available facilities. Most small units for the treatment of tuberculosis should be abandoned in favor of larger and more thoroughly equipped tuberculosis hospitals.

3. Tuberculosis hospitals combining general hospital and sanatorium facilities offer the best opportunities for treatment.

4. There appears to be a real need for standardization of medical records and nomenclature.

5. Greater and more general utilization of tuberculosis hospitals in medical, nursing and public health education is essential to progress.

6. No facts are given in the survey by the American Medical Association to indicate the extent to which the tuberculosis sanatoria and hospitals act as public health educational centres for their communities. When a hospital is located within a reasonably short distance from the people it is intended to serve, such educational activity may become one of the features of its program; otherwise, its contribution in this regard is, of necessity, very limited.

More universal and broader facilities for avocational as well as vocational training and education of patients are urgently needed. Further provision must be made for the reëmployment of all employables who are victims of this disease.

7. Integration of the public hospitals with local health departments in the conduct of local clinics and case-finding programs should be inaugurated wherever possible. From the standpoint of tuberculosis control, the survey reveals that most tuberculosis hospitals maintain

a service restricted for the most part to clinical medicine. Is it not possible that millions of dollars are being spent annually on the end result of the invasion of the tubercle bacilli? From the public health viewpoint, this may be a good expenditure. However, could not the same funds be made to yield larger returns in human economy if our tuberculosis hospital staffs would approach the problem more fundamentally? Is it good medical or good public health practice to tolerate a condition under which 70 per cent of patients are admitted for treatment in an almost hopeless stage of their disease when we have the scientific and administrative means to discover a far greater percentage of cases in the earlier and more hopeful stage of the disease?

Although health departments are commonly charged with the responsibility of community tuberculosis control, the tuberculosis hospital by virtue of its personnel and equipment should assume a conspicuous place in the control program.

By having the sanatoria staffs conduct case-finding and follow-up clinic service, the health department is assured of expert service at a minimum of cost. Such an integrated service provides continuity of medical guidance and assistance from diagnosis to recovery. Anyone who has witnessed the plight of a patient shunted from two to four services offering as many different opinions regarding diagnosis or proposed methods of treatment should well appreciate the value of such continuity.

Although tuberculosis manifests itself clinically in the individual, the causes are to be found in the community. Is it not time for tuberculosis workers to mass all their professional resources and, by well directed effort on all fronts, discover more cases earlier in their disease? They should reduce further the intimacy and duration of contact with sputum-positive cases and thereby realize greater returns. To my mind, the public tuberculosis hospital has its greatest opportunity for service outside its own four walls.

From the above, it is apparent that if further progress in tuberculosis is to be realized, leadership and money are necessary. We must look to the private agencies, health departments and tuberculosis hospitals for leadership. There must be a reawakening of the fervor and enthusiasm which characterized the early days of the antituberculosis campaign. A close integration of the institutions by health departments and tuberculosis hospitals is imperative.

As regards any additional appropriations, it will be necessary, except

in a few sections of the country, to look to the states, or perhaps to some extent to the federal government, for the additional funds necessary to provide an equal opportunity for tuberculosis patients throughout the country.

It must be realized that tuberculosis is commonly found among the underprivileged. Ways and means must be found to assist the deserving families of tuberculous patients financially in a manner which will be free from the stigma of pauperism. If this can be accomplished, then the accruing benefits of our public investment in our tuberculosis control program will be enormously increased. Without financial aid to the family, we can only hope for mediocre results. It would seem futile to expect the further development of facilities to meet our present and future needs unless there becomes available a promotion program objective in vision, economic in purpose and positive in conduct.

The material quoted in this paper is from: PLUNKETT, R. E.: Tuberculosis hospitals and sanatoria in the United States, Hospitals, 1938, *12*, 58–62.

# TUBERCULOUS INFECTION IN KINGSTON, JAMAICA

## A Study Based on X-ray Examinations[1]

C. W. WELLS AND H. H. SMITH

The data accumulated during a tuberculosis survey in Kingston, Jamaica are of particular interest, since they pertain to a representative sample of the population of a tropical city. The population examined comprised, in the main, members of the Negro race, ranging from pure black to light and pale brown in color, with a small group of whites, East Indians and Chinese. One phase of the study included chest X-ray examinations of 4,912 individuals (4,359 tuberculin-positive and 553 tuberculin-negative) representing 69.1 per cent of the total population of the survey areas.

For the purpose of analysis, the lesions demonstrated by the X-ray have been classified as follows:

(a) Manifest pulmonary tuberculosis
  1. Childhood type
  2. Adult type

(b) Latent tuberculosis
  1. Calcified pulmonary nodules
  2. Latent infiltration, childhood type
    (*a*) Soft or flocculent
    (*b*) Strandlike

(c) Tuberculosis of tracheobronchial lymph nodes
  1. Calcified
  2. Massive caseous

(d) Latent apical tuberculosis

The results of the X-ray examinations are presented in this paper under two headings: (*a*) the frequency of tuberculous lesions, by survey

[1] These studies were conducted with the support and under the auspices of the International Health Division of The Rockefeller Foundation, in coöperation with the Jamaican Government Medical Department.

areas, and (*b*) the frequency of tuberculous lesions in relation to race and racial mixtures.

## X-RAY LESIONS ACCORDING TO SURVEY AREAS

The four areas in the city of Kingston selected for a tuberculosis survey were chosen to represent the different economic and social conditions prevailing in the city. Areas 1 and 2 were populated largely by the poorest classes and contained a larger proportion of the uneducated and ignorant classes than the other areas, with many insanitary homes and yards with which was associated overcrowding. Area 3 represented a middle-class population, and area 4 contained a high percentage of the upper middle class with sanitary homes and an absence of overcrowding. At least 95 per cent of the population in areas 1 and 2 lived in yard rooms,[2] while in areas 3 and 4 this was true for less than 5 per cent.

The proportion of black and dark brown individuals differed materially in the four areas, being significantly greater in areas 1 and 2.

*Frequency of tuberculous lesions by survey areas:* A comparison of the frequency of tuberculous lesions by areas cannot be made without some adjustment of the data, due to the fact that X-ray examinations in areas 3 and 4 were restricted to tuberculin-positive reactors. The frequency of lesions among the tuberculin-positive reactors may be discussed according to areas, but the results do not lend themselves to interpretation in terms of the population as a whole and may be misleading since the frequency of positive reactors, particularly in area 4, was less than in the other areas.

Table 1 gives the observed frequencies with lesions for areas 1 and 2. Table 2 gives similar observations for areas 3 and 4, as well as the number of tuberculin nonreactors. These two tables furnish the necessary data for the adjustments in frequencies of lesions for areas 3 and 4 given in table 3. In adjusting the frequencies it was assumed that the percentage of persons with lesions among nonreactors in areas 3 and 4 was the same as that observed in areas 1 and 2 combined. The process of adjustment was quite simple. The frequencies of positive and of negative tuberculin reactors were determined. The percentage of positive reactors in areas

[2] The term "yard room" describes a mode of living common among the poorer classes in certain tropical countries, especially among members of the Negro race, and represents an adaption of the kraal, comprising a number of individual rooms, single or in series, each room occupied by a different family. The number of families living in one yard may vary from two to twenty.

3 and 4 was multiplied by the percentage found with lesions in the corresponding age and sex group. The percentage of negative reactors was multiplied by the percentage found with lesions in areas 1 and 2 for the same group. The two fractions were added to give the adjusted frequencies.

TABLE 1

*Lesions demonstrable by X-ray in tuberculin tested individuals in areas 1 and 2. These data for nonreactors employed in adjusting frequencies for areas 3 and 4*

| AGE | SEX | AREA 1 | | | | | | | | | | AREA 2 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Tuberculin-positive reactors | | | | | Tuberculin-negative reactors | | | | | Tuberculin-positive reactors | | | | | Tuberculin-negative reactors | | | | |
| | | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions |
| *years* | | | | | | | | | | | | | | | | | | | | | |
| 0–4 | M | 38 | | | 4 | 4 | 64 | | | | | 15 | | | 1 | 1 | 36 | | | | |
| | F | 48 | 1 | | 2 | 3 | 60 | | | | | 23 | | | | | 59 | | | | |
| 5–14 | M | 114 | | | 11 | 11 | 50 | | | 2 | 2 | 88 | | | 9 | 9 | 41 | | | | |
| | F | 140 | | | 10 | 10 | 48 | | | | | 76 | | | 2 | 2 | 58 | | | | |
| 15–29 | M | 258 | 7 | | 14 | 21 | 15 | | | | | 138 | 3 | | 3 | 6 | 10 | 1 | | | 1 |
| | F | 473 | 11 | 4 | 22 | 37 | 29 | | | 1 | 1 | 299 | 4 | 5 | 10 | 19 | 37 | | | 1 | 1 |
| 30+ | M | 224 | 5 | 14 | 25 | 44 | 4 | | | | | 137 | 5 | 7 | 7 | 19 | 4 | | | 1 | 1 |
| | F | 362 | 11 | 15 | 24 | 50 | 12 | | | 1 | 1 | 234 | 3 | 6 | 14 | 23 | 10 | | 1 | | 1 |
| Total | M | 634 | 12 | 14 | 54 | 80 | 133 | | | | | 378 | 8 | 7 | 20 | 35 | 91 | 1 | | 1 | 2 |
| | F | 1,023 | 23 | 19 | 58 | 100 | 149 | | | 4 | 4 | 632 | 7 | 11 | 26 | 44 | 164 | | 1 | 1 | 2 |
| Total ..... | | 1,657 | 35 | 33 | 112 | 180 | 282 | | | 4 | 4 | 1,010 | 15 | 18 | 46 | 79 | 255 | 1 | 1 | 2 | 4 |

The percentage of total lesions demonstrable by X-ray examination for each area among tuberculin-positive reactors, when corrected to a standard population, showed a fair degree of uniformity in three of the areas: area 1, 11.3 per cent; area 2, 8.1 per cent; area 3, 9.0 per cent; and area 4, 7.4 per cent (table 3).

The percentages of manifest pulmonary tuberculosis among positive reactors for each area were as follows: area 1, 2.1 per cent; area 2, 1.5

per cent; area 3, 1.1 per cent; and area 4, 0.4 per cent. These differences are significant ($X^2 = 9.96$, $P = 0.019$).

The percentages of latent apical lesions among positive reactors for each area were as follows: area 1, 2.0 per cent; area 2, 1.8 per cent; area 3. 1.4 per cent; and area 4, 4.6 per cent. The differences are highly

TABLE 2

*Lesions demonstrable by X-ray in tuberculin-positive individuals in areas 3 and 4; also the number of tuberculin-negative persons in these areas, the latter data employed in calculating lesion frequencies to permit comparison with areas 1 and 2*

| AGE | SEX | AREA 3 | | | | | | AREA 4 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Tuberculin-positive reactors | | | | | Number of tuberculin-negative individuals | Tuberculin-positive reactors | | | | | Number of tuberculin-negative individuals |
| | | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | | Number X-rayed | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | |
| *years* | | | | | | | | | | | | | |
| 0–4 | M | 26 | | | 1 | 1 | 57 | 3 | | | | | 27 |
| | F | 24 | | | | | 37 | 8 | | | | | 22 |
| 5–14 | M | 99 | | | 5 | 5 | 62 | 29 | | 1 | 1 | 2 | 39 |
| | F | 110 | 1 | | 14 | 15 | 66 | 29 | | | | | 45 |
| 15–29 | M | 158 | 1 | 1 | 5 | 7 | 14 | 77 | | 1 | | 1 | 13 |
| | F | 303 | 6 | 2 | 20 | 28 | 39 | 182 | 4 | 1 | 4 | 9 | 27 |
| 30+ | M | 143 | 3 | 4 | 11 | 18 | 5 | 62 | | 9 | 4 | 13 | 2 |
| | F | 278 | 2 | 9 | 20 | 31 | 9 | 153 | | 13 | 8 | 21 | 6 |
| Total | M | 426 | 4 | 5 | 22 | 31 | 138 | 171 | | 11 | 5 | 16 | 81 |
| | F | 715 | 9 | 11 | 54 | 74 | 151 | 372 | 4 | 14 | 12 | 30 | 100 |
| Total ..... | | 1,141 | 13 | 16 | 76 | 105 | 289 | 543 | 4 | 25 | 17 | 46 | 181 |

significant ($X^2 = 19.88$, $P = 0.000$) because of the higher frequency in area 4.

The percentages of latent tuberculosis, childhood type, among tuberculin-positive reactors were as follows: area 1, 6.8 per cent; area 2, 4.6 per cent; area 3, 6.7 per cent; and area 4, 3.1 per cent. These differences are significant ($X^2 = 14.36$, $P = 0.003$).

This study permits a grouping of lesions for further comparison between areas. Cases of manifest tuberculosis in most instances may

be subdivided into those of childhood and those of adult type. Cases of manifest pulmonary tuberculosis, childhood type, may be added to latent tuberculosis, childhood type. The percentages on this basis were as follows: area 1, 7.1 per cent; area 2, 4.6 per cent; area 3, 6.8 per cent; area 4, 3.1 per cent. These differences are highly significant ($X^2 = 16.39$, $P = 0.003$). The differences found in percentages between areas, when latent apical lesions and manifest pulmonary tuberculosis, adult type, were combined, were not significant.

The high frequency of latent apical lesions in area 4 was found in persons over 30 years of age (10.2 per cent). In the other areas the percentages for persons over 30 were much lower: area 1, 4.9 per cent; area 2, 3.5 per cent; area 3, 3.1 per cent. The difference between area 4 and the other three areas combined is significant.

The previous discussion has dealt with the frequency of tuberculous lesions in tuberculin-positive individuals. As such it concerns a highly selected portion of the population and does not reveal a true picture of the occurrence and distribution of tuberculous lesions in the general population. Consequently certain adjustments were made in the frequencies for areas 3 and 4; the method was described above and the results as well as the observed frequencies for areas 1 and 2 are shown in table 3.

This table indicates a higher frequency of tuberculous lesions for area 1 than for any of the other areas. This is true of each age group as well as of the total for all ages. Area 1 also led in the amount of manifest pulmonary tuberculosis. Latent apical lesions were found two or three times as often in area 4 as in any of the other areas.

In area 1 there was a higher frequency of lesions among males than among females in all age groups. In the other areas lesion frequencies were higher among females 15 to 29 years of age. For persons over 30 years of age the frequency was consistently higher among males.

In all areas lesion frequency increased with age. With the exception of one latent apical lesion in a child in the 10 to 14 year group, all lesions in persons under 15 years of age were of the childhood type, two of which were manifest. All types of lesions were found in the older age groups, the latent childhood type giving place to latent and manifest disease of the adult type.

### X-RAY LESIONS IN RELATION TO RACE AND RACIAL MIXTURES

It has been shown that definite differences in the frequency of demonstrable tuberculous lesions were found in the four survey areas in Kings-

TABLE 3

*Frequency percentage of manifest pulmonary tuberculosis, latent apical lesions, latent childhood tuberculosis and total lesions, by age and sex, for each survey area, for all individuals tuberculin tested*

| AGE | SEX | AREA 1 | | | | AREA 2 | | | | AREA 3* | | | | AREA 4* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions |
| *years* | | | | | | | | | | | | | | | | | |
| 0–4 | M | | | 3.77 | 3.77 | | | 1.89 | 1.89 | | | 1.24 | 1.24 | | | | |
| | F | 0.92 | | 1.83 | 2.75 | | | | | | | | | | | | |
| 5–14 | M | | | 7.83 | 7.83 | | | 6.87 | 6.87 | | | 3.96 | 3.96 | | 1.55 | 2.76 | 4.31 |
| | F | | | 5.18 | 5.18 | | | 1.49 | 1.49 | 0.57 | | 7.98 | 8.55 | | | | |
| 15–29 | M | 2.81 | | 4.91 | 7.72 | 2.63 | | 1.97 | 4.61 | 0.89 | 0.58 | 2.92 | 4.40 | 0.46 | 1.15 | | 1.61 |
| | F | 2.18 | 0.79 | 4.55 | 7.52 | 1.46 | 1.46 | 3.21 | 6.12 | 1.77 | 0.59 | 6.21 | 8.57 | 0.98 | 0.49 | 2.29 | 3.75 |
| 30+ | M | 2.56 | 5.98 | 10.68 | 19.23 | 2.08 | 4.86 | 5.56 | 12.50 | 2.04 | 2.71 | 7.83 | 12.58 | | 14.15 | 6.60 | 20.75 |
| | F | 2.88 | 3.93 | 6.81 | 13.61 | 2.45 | 2.86 | 6.12 | 11.43 | 0.70 | 3.27 | 7.12 | 11.09 | | 8.37 | 5.21 | 13.58 |
| Total | M | 1.77 | 1.77 | 7.08 | 10.62 | 1.46 | 1.46 | 4.37 | 7.29 | 0.83 | 0.90 | 4.28 | 6.01 | 0.12 | 4.67 | 2.49 | 7.28 |
| | F | 1.93 | 1.60 | 5.13 | 8.66 | 1.36 | 1.49 | 3.47 | 6.32 | 1.06 | 1.33 | 6.45 | 8.84 | 0.44 | 3.13 | 2.81 | 6.38 |
| Total ..... | | 1.87 | 1.67 | 5.91 | 9.44 | 1.40 | 1.48 | 3.81 | 6.68 | 0.95 | 1.18 | 5.59 | 7.72 | 0.33 | 3.65 | 2.70 | 6.68 |
| Per cent corrected to a standard population based on tuberculin-positive reactors..... | | | | | 11.3 | | | | 8.1 | | | | 9.0 | | | | 7.4 |

* Adjusted to total population given tuberculin tests.

ton. These areas differed significantly in social and economic conditions, as well as in variations in the racial distribution of the population. It is not possible to determine with exactness the influence of these several factors on the occurrence of tuberculous lesions. An analysis of the frequency of lesions on the basis of racial groups has been undertaken, dividing the population of the four areas into four classes according to racial mixture: black, dark brown, light and pale brown, and others. The last group comprises whites, Chinese and East Indians. The distribution of the population on this basis is shown in table 4.

The influence of racial mixture on the frequency of tuberculous infection and disease, as revealed by X-ray examination, is shown in table 5. These frequencies have been adjusted to the total population tuberculin tested as described above. The frequency of lesions among persons in the Negro groups varied only slightly. There was more manifest tuber-

TABLE 4

*Percentage distribution of the survey population by race and racial mixtures*

| | AREA 1 | AREA 2 | AREA 3 | AREA 4 |
|---|---|---|---|---|
| Black | 59.2 | 30.4 | 18.1 | 23.7 |
| Dark brown | 28.2 | 46.5 | 35.3 | 20.3 |
| Light and pale brown | 6.6 | 18.8 | 42.3 | 39.2 |
| Others | 5.9 | 4.3 | 4.3 | 16.8 |

culosis among black individuals, and a somewhat higher frequency of latent apical lesions among light and pale brown persons. The only real difference shown by the table is that between latent apical lesions among whites, Chinese and East Indians and the Negro groups. The higher frequency for the group designated "others" becomes more marked when age is taken into account since these lesions were confined to persons over 30 years of age.

The results that have been obtained give no conclusive evidence that racial mixture is the determining factor influencing the amount or character of tuberculous infection. The higher frequency of latent apical lesions in light and pale brown individuals and "others" on the one hand may be the result of better living conditions as it occurred chiefly in areas 3 and 4, whereas the predominance of manifest tuberculosis among black persons may have been associated with unfavorable living conditions in area 1.

TABLE 5

*Frequency percentage of manifest pulmonary tuberculosis, latent apical lesions, latent childhood tuberculosis and total lesions, by age and sex, for each color group (adjusted to total population given tuberculin tests)*

| AGE | SEX | BLACK | | | | DARK BROWN | | | | LIGHT AND PALE BROWN | | | | OTHERS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions | Manifest pulmonary tuberculosis | Latent apical | Latent childhood | Total lesions |
| *years* | | | | | | | | | | | | | | | | | |
| 0–4 | M | | | 2.16 | 2.16 | | | 3.49 | 3.49 | | | 1.54 | 1.54 | | | | |
| | F | 1.40 | | | 1.40 | | | 0.88 | 0.88 | | | | | | | 1.03 | 1.03 |
| 5–14 | M | | 0.58 | 6.19 | 6.77 | | | 6.78 | 6.78 | | | 1.50 | 1.50 | | | 11.26 | 11.26 |
| | F | | | 3.80 | 3.80 | 0.46 | | 5.95 | 6.41 | | | 3.10 | 3.10 | | | 6.73 | 6.73 |
| 15–29 | M | 2.52 | | 4.24 | 6.77 | 0.50 | | 3.02 | 3.52 | 0.28 | 0.14 | 0.21 | 0.63 | | | | |
| | F | 2.09 | 0.42 | 3.52 | 6.02 | 1.41 | 1.21 | 4.34 | 6.95 | 1.42 | 1.14 | 5.12 | 7.68 | 1.80 | | 5.40 | 7.20 |
| 30+ | M | 1.60 | 5.20 | 9.77 | 16.57 | 1.19 | 3.57 | 8.34 | 13.11 | 1.80 | 7.21 | 4.51 | 13.52 | 3.93 | 13.77 | 11.80 | 29.51 |
| | F | 2.11 | 3.43 | 6.08 | 11.63 | 1.93 | 3.74 | 7.04 | 12.71 | 1.47 | 5.52 | 5.89 | 12.89 | | 6.03 | 6.03 | 12.07 |
| Total | M | 1.39 | 1.71 | 5.99 | 9.09 | 0.48 | 0.95 | 5.56 | 6.99 | 1.33 | 2.22 | 2.45 | 6.01 | 1.52 | 5.31 | 7.59 | 14.42 |
| | F | 1.74 | 1.38 | 4.18 | 7.30 | 1.26 | 1.63 | 5.12 | 8.01 | 1.05 | 2.21 | 4.54 | 7.80 | 0.69 | 2.08 | 6.23 | 9.00 |
| Total. . . . . | | 1.59 | 1.52 | 4.96 | 8.08 | 0.99 | 1.41 | 5.29 | 7.68 | 1.15 | 2.22 | 3.82 | 7.18 | 1.09 | 3.62 | 6.88 | 11.59 |

## SUMMARY AND CONCLUSIONS

A study of tuberculosis in the city of Kingston, Jamaica by X-ray examination disclosed the relationship of social, economic, hygienic and racial factors to the occurrence of tuberculous infection and disease in a population living under tropical conditions.

Manifest pulmonary tuberculosis was found in 1.87 and 1.40 per cent of persons in the two poorest areas, in 0.95 per cent in the intermediate, and in only 0.33 per cent in the most prosperous area.

A significant difference was found in the frequency of latent (asymptomatic) apical tuberculosis in the four surveyed areas, the greatest frequency (3.65 per cent) being found in the most prosperous area, where light brown, pale brown, and white persons were most numerous. Latent lesions of childhood type were on the contrary much less frequent in this than in other areas; these observations indicate that infection in the prosperous area occurred less frequently in children and when it occurred in adults was more likely to heal.

Analysis on the basis of racial mixture showed that manifest pulmonary tuberculosis was most frequent in the black, and latent apical lesions in the pale brown, but it has not been possible to determine whether these differences are hereditary or environmental.

The authors wish to acknowledge the assistance rendered by Dr. Persis Putnam in connection with certain details of the statistical work contained in this paper.

# FLUOROSCOPY DURING PNEUMOTHORAX TREATMENT[1]

## An Important Aid in the Treatment of Difficult Cases

LOUIS COHEN AND JOHN V. BLADY

An experience of eleven years with a large number of pneumothorax cases at Eagleville Sanatorium, Eagleville Dispensary and Temple University Hospital has given one of us (L. C.) the opportunity of seeing many patients in whom an occasional pneumothorax refill, in a hitherto easy or well established case, unexpectedly turns out to be difficult or impossible. When this happens the operator usually makes several needle punctures at different sites in the chest in an effort to find the pneumothorax pocket, and he may or may not be successful. In any event, the patient is subjected to multiple needle punctures, and often there may be untoward effects such as shock, lung puncture, haemoptysis, and even the establishment of a pneumothorax with untoward pressure effects. Frequently a case must be discontinued because the operator, after several attempts to refill, cannot locate the pleural space and is forced to abandon the collapse.

This type of difficult refill suggested to one of us (J. B.) the possibility of giving pneumothorax refills directly under fluoroscopic guidance. We gave our first refill under fluoroscopic guidance at Temple University Hospital on March 3, 1935 to a patient who had had three unsuccessful attempts at refilling in the regular clinic that day. Because of these difficulties the patient was studied fluoroscopically in the upright and in the lateral decubitus positions; at once it was seen that the most favorable site for the introduction of the pneumothorax needle was at the costophrenic angle, where the space between the visceral and parietal pleurae was greatly increased with the patient in the lateral decubitus position. Under fluoroscopic guidance the needle was introduced at this point and the treatment successfully given. The pneumothorax was thereafter easily continued in the regular clinic.

Our success in this particular case led us to carry out further investigation of this procedure so that its usefulness could be properly evaluated. We published an account of this procedure (3) and since then

[1] From the Departments of Roentgenology and Medicine, Temple University Medical School, Philadelphia, and the Eagleville Sanatorium, Eagleville, Pennsylvania.

we have continued working along the following lines: (*1*) comparison of the roentgen appearance of the pneumothorax in the upright and lateral decubitus positions; (*2*) further studies on administration of artificial pneumothorax under fluoroscopic guidance; (*3*) fluoroscopic observations on the behavior of the thoracic viscera during the administration of the treatment in initial and refill cases; and (*4*) consideration of the factors involved in the phenomenon of so called "selective pneumothorax."

## TECHNIQUE

The procedures and necessary equipment have been described in our original publication dealing with this work (3). The ordinary upright fluoroscope or the biplane are equally adaptable to the carrying out of this procedure.

The fluoroscopic study in the upright position is made by gradually rotating the patient from zero to 180° so that the position or positions of choice, demonstrating the relation of the collapsed lung to the pneumothorax to best advantage, is determined for each patient individually. The patient then lies on a stretcher on the unaffected side (lateral decubitus) with a pillow under the axilla and the diseased side of the chest is fluoroscoped using the horizontal ray. The stretcher can readily be manipulated so that it will not interfere with the movable supporting arm of the fluoroscopic screen or with the screen itself. Here again the patient is rolled 45° to either side of the true lateral and observed fluoroscopically. The same general precautions are to be observed during the fluoroscopy of a pneumothorax patient as are observed in any other fluoroscopic examination, namely, a survey of the entire chest should first be made utilizing the entire screen (wide aperture) and than a further study is carried out with a small aperture for particular details.

It is extremely important that the fluoroscopist have sufficient eye adaptation before attempting a study of a pneumothorax patient because in many cases it is difficult to ascertain the fine visceral pleural markings and adhesions. For this reason fifteen to twenty minutes are spent for eye adaptation.

An ordinary flash light fitted with a red filter or red cellophane provides sufficient illumination for preparing the skin and for the operator to observe the manometric oscillations and the amount of fluid in the bottles without disturbing the adaptation of the fluoroscopist. The

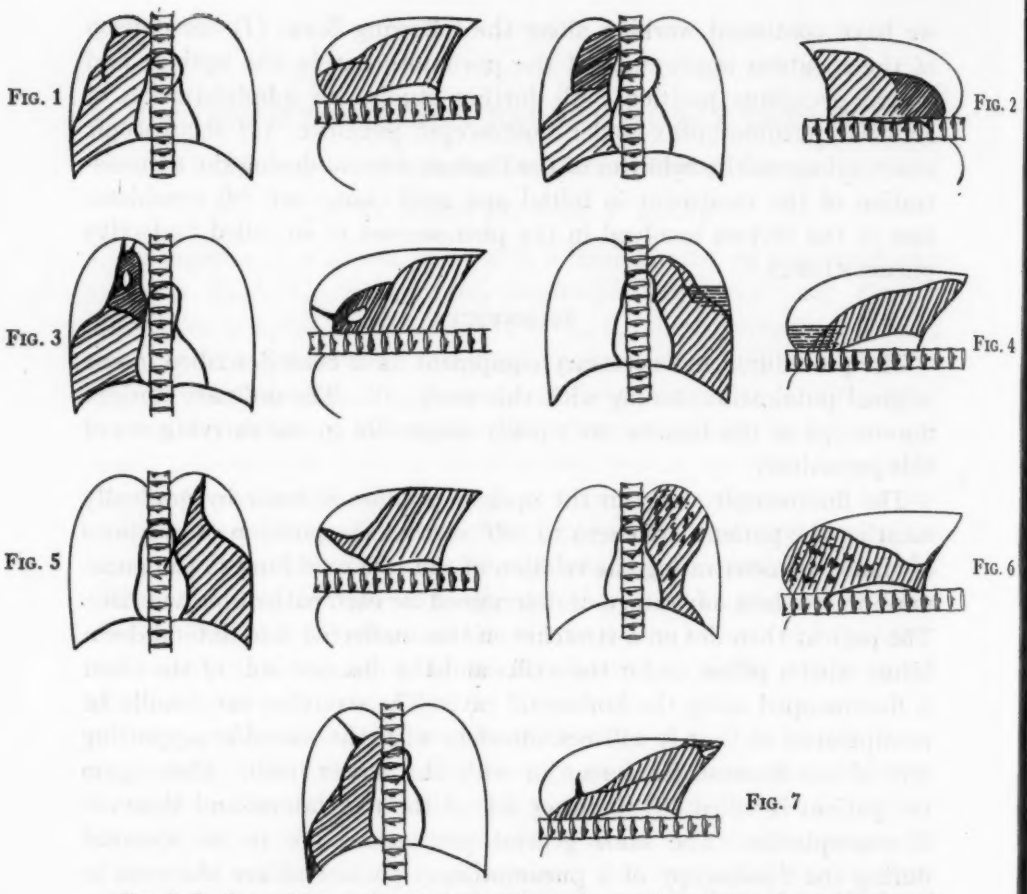



FIG. 1. In the upright tracing (ventral projection) a partial collapse of the right lung is observed and the lung is in contact with the thoracic wall at the base. In the lateral decubitus, however, (dorsal projection) no part of the lung is seen in contact with the chest-wall and the pneumothorax extends from the apex to the costophrenic angle.

FIG. 2. In the upright drawing (ventral projection) there is a "selective collapse" of the right upper lobe while the lower and middle lobes are partially collapsed and are in contact with the chest-wall. In the left lateral decubitus (ventral projection) the lower and middle lobes fall away from the chest-wall and the pneumothorax extends to the costophrenic angle.

FIG. 3. As in fig. 2, practically the same findings are observed. All three cases (figs. 1, 2, & 3) illustrate the position change which occurs when the patient is placed in the lateral decubitus.

FIG. 4. Both diagrams are ventral projections. A partial collapse of the left lung with fluid overlying the expanded portion of the lung is demonstrated. These findings are suggestive of adhesions obliterating the pleural space. However, when the patient is placed in the lateral decubitus the fluid gravitates to the apex and the entire left lung falls away from the chest-wall and the pneumothorax extends from the apex to the costophrenic sulcus. This is a most important demonstration of an unobliterated pleural space.

light should be so arranged as not to cast a direct beam on the screen as this interferes with fluoroscopic acuity.

FIG. 2 After the most suitable site for the insertion of the needle has been selected fluoroscopically, the skin is prepared and draped as for any other surgical procedure. Local anaesthesia is employed in every case. Then under fluoroscopic guidance the needle is introduced into the pleural space and its position is always carefully observed, especially in those cases in which the needle is introduced at the costophrenic angle or into a very small pneumothorax pocket elsewhere.

FIG. 4 To protect the operator's hand from exposure to the primary beam we have devised a lead shield which is readily attached to the operator's arm and offers adequate protection to the fingers of the hand in case they may be exposed momentarily to the primary beam. In addition to this precaution we have made it a practice to use as small an aperture as possible and to keep the operator's hand out of the beam at all times. In this connection it is advisable also to consider the radiation delivered

FIG. 6 to the skin of the patient. Though the roentgen output for such a fluoroscopic study is minimal, we avoid any unnecessary prolongation of the fluoroscopic procedure.

## ROENTGEN STUDIES ON THE PNEUMOTHORAX IN THE VERTICAL AND LATERAL DECUBITUS POSITIONS

A total of 146 individual position studies was made to determine the changes that occur within the pneumothorax chest. On all of these cases fluoroscopic tracings, and in some cases roentgenograms, were made in both the vertical and lateral decubitis positions.

Our results, after careful comparison of the pneumothorax patient in these two positions, indicate that definite changes in the position of

---

FIG. 5. Both diagrams are ventral projections. The appearance and position of the partially collapsed left lung remains unchanged when the patient is placed in the lateral decubitus, indicating obliteration of the pleural space and adherence of the two pleural surfaces. Compare with figs. 1, 2 & 3.

FIG. 6. Both diagrams are ventral projections. The diagrams are self-explanatory. The upper lobe is adherent at the apex and altering the position of the patient produces no change whatever in the position of this portion of the lung. In the lateral decubitus, however, the lower lobe is displaced slightly medially and a larger basilar pneumothorax is noted.

FIG. 7. Note the lower lobe adhesions. No appreciable change was noted in the appearance of the collapsed lung when the patient lay on the uneffected side; the adhesions prevented any change in the position of the partially collapsed lung.

FIG. 8

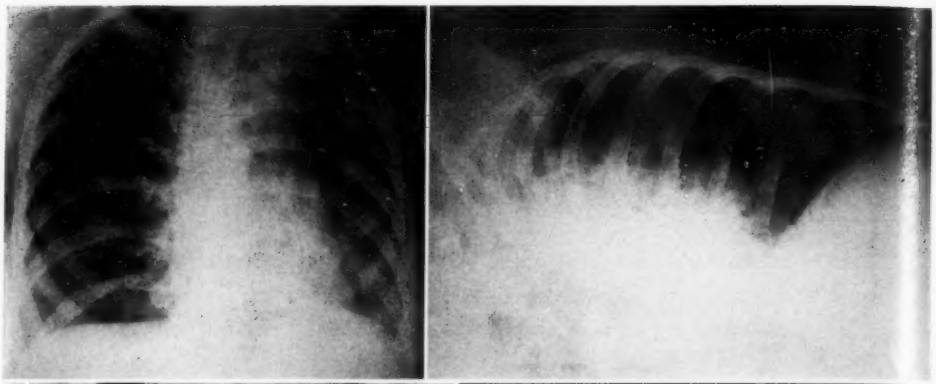


FIG. 9

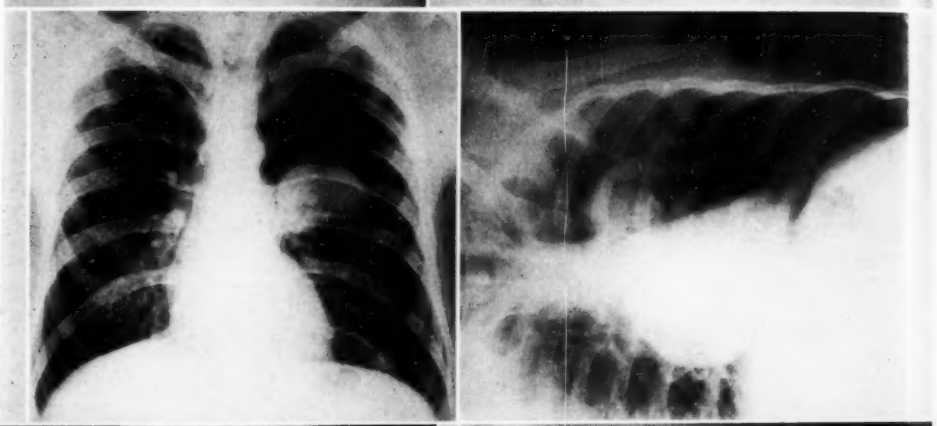


FIG. 10

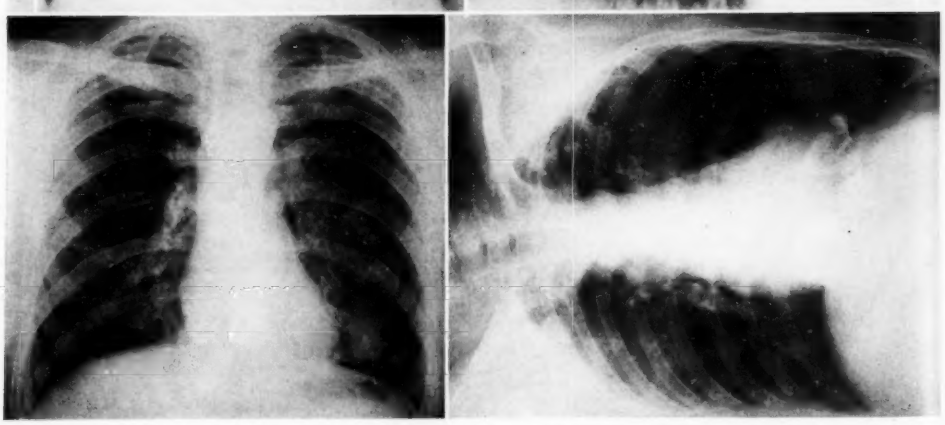


FIG. 8. The upright roentgenogram is a dorsal projection; the left lateral decubitus is a ventral projection. A "selective collapse" of the right upper lobe is present; the lower and middle lobes are partially collapsed and are in contact with the thoracic wall at the level of the 9th and 10th ribs. In the lateral decubitus position the pneumothorax extends from the apex to the costophrenic angle.

the collapsed lung occur when the patient is placed in the lateral decubitus position. The upright fluoroscopic tracings and films do not always offer the maximum information regarding the condition, position and mobility of the lung, the extent of the pneumothorax and the presence or absence of adhesions at the base or along the chest-wall. The changes that actually occur when a patient is placed from the vertical position to the lateral decubitus are best demonstrated by fluoroscopic tracings and film records in figures 1 to 10 inclusive. In figures 1, 2, 3, 8 and 9, the differences between the upright and lateral decubitus studies are readily noted. In all cases in the vertical position the lower lobe was found to be in contact with the lateral chest-wall; the lateral decubitus position, on the other hand, revealed an entirely mobile, nonadherent lower lobe in each case. This latter condition of the lower lobe permitted the partially collapsed lung to gravitate with the change in position and displaced the pneumothorax to a new position along the lateral chest-wall from the apex to the costophrenic angle.

On comparing the upright study in figures 1, 2, 3, and 5 the similarity of appearance of the partially expanded lower lobe and the pneumothorax is noted. In figure 5, however, the lateral decubitus study definitely established the fact that the lung was adherent to the chest-wall.

In figure 4 another situation was encountered. The upright study revealed a partial apical collapse with fluid overlying the expanded lung; heretofore, this roentgen appearance was usually interpreted as indicating a reëxpanding lung or obliterating pneumothorax. Here, however, the lateral decubitus study revealed an unobliterated pleural space although the lung was quite markedly expanded. We believe that this roentgen appearance is produced by fibrinous adhesions. Further observation regarding this interesting phenomenon are noted in the next section.

---

Note the separation of the lung from the diagram at the costophrenic angle thereby increasing the pneumothorax pocket in this region. (Compare with figs. 1, 2 & 3.)

FIG. 9. Both roentgenograms are dorsal projections. Atelectasis of the left upper lobe is observed while the lower lobe is expanded and is in contact with the thoracic wall. In the lateral decubitus, however, the lower lobe has gravitated away from the chest-wall. The pneumothorax extends to the costophrenic sulcus. (Compare with figs. 1, 2 & 3.)

FIG. 10. Both roentgenograms are dorsal projections. The lateral decubitus study reveals a slight increase in the pneumothorax at the costophrenic angle. Note how the diaphragm has been pulled taut by the displaced lung and heart. (Compare with fig. 6.)

ADMINISTRATION OF PNEUMOTHORAX UNDER FLUOROSCOPIC GUIDANCE

The administration of artificial pneumothorax under fluoroscopic guidance is not a routine procedure. It should be reserved for the difficult case which is occasionally encountered in every large clinic. As a routine procedure it is time consuming and the frequent exposure of the patient to roentgen rays, even though very slight but continued over a long period of time, may be hazardous and, therefore, should be avoided.

Up until January 1, 1936 we attempted fluoroscopic guidance in 86 cases and have successfully administered refills in 80 cases and induced pneumothorax in two initial cases. There were four failures; two of which were due to obliterative phenomena of more than a month's duration and the other two were initial cases with widespread disease and thickened pleura demonstrated on the roentgenograms.

| | | |
|---|---|---|
| Refill treatments... | 82 cases | |
| Successful..... | 80 cases | (12 under biplane fluoroscopic guidance; 68 under ordinary upright fluoroscope, utilizing horizontal ray) |
| Unsuccessful.... | 2 cases | (both had reëxpanded and obliterated over a month prior to attempt at refill under fluoroscopic guidance) |
| Initial—only 4 cases attempted | | |
| Successful..... | 2 cases | |
| Unsuccessful.... | 2 cases | (both had previously been tried in regular clinic) |

In this method of treatment the lateral decubitus study is of the greatest importance. The accepted method of giving pneumothorax refills is to have the patient lie on the unaffected side. Likewise, it seems that the universally accepted method has been to carry out the roentgenographic examination of the pneumothorax patient in the upright position. In other words, the study is not made in the same position in which treatment is given. In the relatively easy cases this procedure is acceptable; however, the difficult cases should always be given the benefit of study in the lateral decubitus in an effort to find the cause of the difficulty. It is essential for a better understanding of the actual difficulties that are present or that one may encounter in administering the refill treatment.

The following indications, we consider, deserve the lateral decubitus fluoroscopic study to determine whether fluoroscopic guidance should be utilized during the administration of the refill:

(*1*) Inability to find the pleural space
(*2*) The presence of air loculi
(*3*) The presence of adhesions at site of needle puncture
(*4*) All cases of haemoptysis following treatment
(*5*) Patients who have missed treatment and have lost collapse
(*6*) In cases where the pneumothorax is beginning to obliterate
(*7*) In any case in which the treatment is hazardous and might be given with greater ease through another site

The technique, described previously (3), is exceedingly simple and requires no additional equipment other than the upright fluoroscope and a stretcher.

Each pneumothorax is an individual problem and likewise the position of choice for the insertion of the needle has to be determined for each patient individually by a thorough study in lateral decubitus. The pneumothorax needle may be safely introduced into the chest at practically any point under fluoroscopic guidance. In one of our patients (case 2) the fifth interspace, in a midscapular or paravertebral plane, was selected and to date has been successfully used in the regular outpatient clinic with less hazard to patient and with no untoward sequelae.

The commonest and most suitable site for the insertion of the needle under fluoroscopic guidance is the costophrenic angle. In patients in whom the caudal half of the lung is not adherent, the lateral decubitus position will reveal a good sized pneumothorax at the costophrenic angle, even though this is not seen in the upright study. The location is usually at the tenth or eleventh interspace at any point in a plane between the anterior and the posterior axillary lines. In this region the subcutaneous and muscular tissues are minimal in thickness and hence the needle puncture is less traumatizing. About 90 per cent of our cases were treated through this site.

The proximity of the needle to the diaphragm must be carefully observed as the diaphragm is oftentimes not more than one-half to one inch from the point of the needle and during inspiration may even be nearer. However, after the inflation of 100 cc. of air, the diaphragm is depressed and there is very little danger of its becoming injured. Two of the illustrations (figures 23 and 24) show the needle in relation to the diaphragm and the collapsed lung at this site. In one of our cases (case 10, figure 20) we observed the needle in contact with the diaphragm on two different occasions and following each of these treatments the patient experienced diaphragmatic pain for about 48 hours. Un-

doubtedly the diaphragm during its excursions was lacerated by the point of the needle.

In several patients the fluoroscopic study showed the lung adherent along the dorsal chest-wall and a large pneumothorax pocket ventral to it or *vice versa*. On the other hand, single anteroposterior or postero-anterior fluoroscopic tracings and roentgenograms in the upright position did not convey this information to the operator. This explains how easily such an adherent lung could be punctured when this situation exists and is unknown to the operator. In this type of case a refill under fluoroscopic guidance is of the greatest help and it is seldom necessary to give more than one or two treatments with fluoroscopic aid as the operator soon becomes acquainted with the individual difficulties and subsequent fluoroscopic tracings in lateral decubitus made before each treatment will furnish the necessary information.

One of the most gratifying results of this work was the reëstablishment of a pneumothorax in a patient who had reëxpanded and partially obliterated. Heretofore, treatment in this type of patient was discontinued and, if the disease was still active, radical surgery was advised. To date, we have had the opportunity to study only one such case (case 12, figure 22). In this patient we succeeded in reëstablishing a collapse although extensive pleuritis of the lower half of the lung prevented collapse of this part. Under continued treatment, however, we have noticed that the area of adhesive pleuritis has surprisingly decreased in size, and string and band adhesions have formed. We believe that eventually these adhesions will stretch and elongate and a partial and better collapse of this lung will be obtained.

A very frequent cause of difficulty in the administration of refills is the formation of fibrinous adhesions between the visceral and parietal pleurae. In five of our cases (cases 1, 3, 9, 10 and 11) direct proof of the presence of such adhesions is demonstrated not only clinically but radiographically. In all these cases the pleural cavity was not located and in several cases as many as three unsuccessful chest punctures were attempted. In two of the cases blood spitting followed the treatments (cases 9 and 11). The study in lateral decubitus in these patients demonstrated an expanded and adherent lung. In four patients (cases 1, 3, 9 and 10) a small pneumothorax was observed at the costophrenic angle while the lung above this point was found in contact with the thoracic wall in the lateral decubitus position, and, therefore, definitely adherent. During the administration of the treatment fluoroscopic

observation revealed the gradual separation of the two pleural surfaces, whereas in cases where the lung was in contact but not adherent to the thoracic wall the collapse of the lung occurred more simultaneously and uniformly over the entire nonadherent lung. In one patient (case 1) a complete separation of the two pleural surfaces was not accomplished during the treatment but occurred at the time of fluoroscopy in the erect position shortly after the treatment.

The demonstration of the presence of these adhesions explains not only the inability to locate the pleural cavity but also the ease with which the lung may be injured. If treatment is successfully given to these patients, and this depends on finding a pneumothorax pocket, these adhesions are readily destroyed and separated and the pneumothorax is reëstablished; however, if treatment is not given fibrous adhesions replace the fibrinous type and a permanent obliteration of either a part or of the entire pleural cavity results.

The knowledge that this fluoroscopic procedure offers an indispensable aid in the treatment of our difficult cases has prompted us to establish a fluoroscopic pneumothorax clinic, to which only difficult cases are referred. In our regular pneumothorax clinic, our rule is not to subject a patient to more than one unsuccessful puncture. If the pleural space is not located on the first attempt, there is a reason or reasons for the failure and the patient is referred for a complete fluoroscopic study in lateral decubitus. The difficulty is usually readily explained by this study and the fluoroscopist advises as to the best site for needle puncture or suggests that treatment be done under fluoroscopic guidance. All our cases are subjected at intervals to a thorough fluoroscopic study in lateral decubitus in addition to the upright position.

It is our belief that this study in lateral decubitus not only acquaints us better with the pneumothorax of our patients, but will aid in detecting early changes which doubtless would not be observed in the upright position alone. The possession of these additional procedures has given us a feeling of safety and assurance about difficult cases which we never enjoyed before.

We have found fluoroscopic guidance of no great value in performing initial pneumothoraces. However, in determining the best site for the introduction of the pneumothorax needle in an initial case, the area of least pleural involvement should be localized by either a complete roentgenographic examination or by fluoroscopy, as this offers the best chance of finding an unobliterated pleural space.

## CASE REPORTS

The following illustrated cases present some of the interesting, unusual and puzzling problems in the diagnosis and treatment of the difficult pneumothorax, which with the aid of the study in lateral decubitus were explained and were successfully treated under fluoroscopic guidance during the administration of the refill.

*Case 1:* (J. G.) This patient was under artificial pneumothorax treatment for approximately four years. In March, 1935, in spite of an apparently good upright fluoroscopic tracing, the pneumothorax could not be located. Three times the pneumothorax needle was inserted through the chest-wall unsuccessfully. Because of this, the patient was referred for special fluoroscopic study. The pneumothorax was confined to the anterior and anterior axillary portions of the pleural cavity. The lateral decubitus revealed pneumothorax pockets at the apex and at the costophrenic angle. Several consecutive refills were given at the costophrenic angle under fluoroscopic guidance and then the patient was referred back to the outpatient clinic. In October, 1935, because of failure to locate the pleural space, the patient was again referred to the fluoroscopic pneumothorax clinic. At this time the upright tracing revealed the caudal half of the right lung in contact with the chest-wall in the axillary line. In the lateral decubitus this portion of the lung was found adherent to the chest-wall; at the costophrenic angle, however, a small pneumothorax pocket was visualized. Under fluoroscopic guidance the refill treatment was administered through this site and an excellent collapse was obtained. The adherent lung gradually separated from the chest-wall except for a portion which remained adherent above the costophrenic angle. When the patient was studied in the upright posture, immediately after the treatment, the lung was seen to fall away from the chest-wall.

This case illustrates the presence of fibrinous adhesions between the two pleural parietes and how readily these may be separated by pneumothorax. There has been no further difficulty and the patient is receiving refills at the regular outpatient clinic. (See figures 11A, B, C, D.)

*Case 2:* (E. M.) This patient has a bilateral pneumothorax; on the left side the pneumothorax has been continued for three years while on the right for one year.

On October 23, 1935 the operator experienced difficulty in locating the pleural space on the left side. Fluoroscopy in the lateral decubitus position revealed that the entire lung was found in contact with the chest-wall except for a small pocket of pneumothorax at the costophrenic sulcus, measuring approximately 3 to 4 cm. in width and 6 to 7 cm. in length.

Under fluoroscopic guidance the pneumothorax needle was introduced into

this pocket (figure 23) and 300 cc. of air was injected without difficulty. The resulting partial collapse was satisfactory. Practically the entire lung peeled away from the chest-wall except for a portion above the costophrenic angle in the axillary line where the lung was densely adherent. (See figures 12A, B, C, D.)

*Case 3:* (M. J.) This patient had been under pneumothorax treatment for approximately six months and had never presented any difficulty. On October 23, 1935 the diagram in upright posture (figure 13A) showed a partial collapse of the left lung with the pneumothorax pocket extending from the apex along the axillary line to a point midway between the costophrenic angle and the axilla. The study in lateral decubitus position (figure 13B) demonstrated a small pocket of air at the costophrenic sulcus, above which the lung was attached to the chest-wall. At the level of the axilla and at the apex a large pneumothorax space was seen. This fluoroscopic finding explained the reason for the difficulty in locating the pleural space. Apparently the pneumothorax needle would strike the adherent lung and consequently the pleural space was not located.

Under fluoroscopic guidance the needle was introduced at the costophrenic angle and the treatment was administered without difficulty. During the refill the lung was observed to peel away slowly from the chest-wall and a satisfactory collapse was obtained.

The patient received three treatments under fluoroscopic guidance and after a satisfactory pneumothorax was reëstablished and maintained the patient was sent back to the dispensary for further refills in the regular clinic. (See figures 13A, B, C, D.)

*Case 4:* (J. M.) Artificial pneumothorax has been maintained for three years. On November 1, 1935 in spite of a favorable fluoroscopic tracing in upright position, the operator did not find the pneumothorax after inserting the needle in the usual site between the anterior and midaxillary lines. Only one attempt was made and the patient was referred to the fluoroscopic pneumothorax clinic.

Fluoroscopy revealed no evidence of pneumothorax when patient was placed in left lateral decubitus, left anterior oblique position (figure 14B). The right anterior oblique (100°–110°) (figure 14C), on the other hand, showed a large pneumothorax pocket indicating that the lung was expanded along the ventral chest-wall.

The treatment was successfully administered through the fifth interspace, in the posterior axillary line. Since then this new site has been used and the treatments have been successfully carried out in the regular pneumothorax refill clinic. (See figures 14A, B, C, D.)

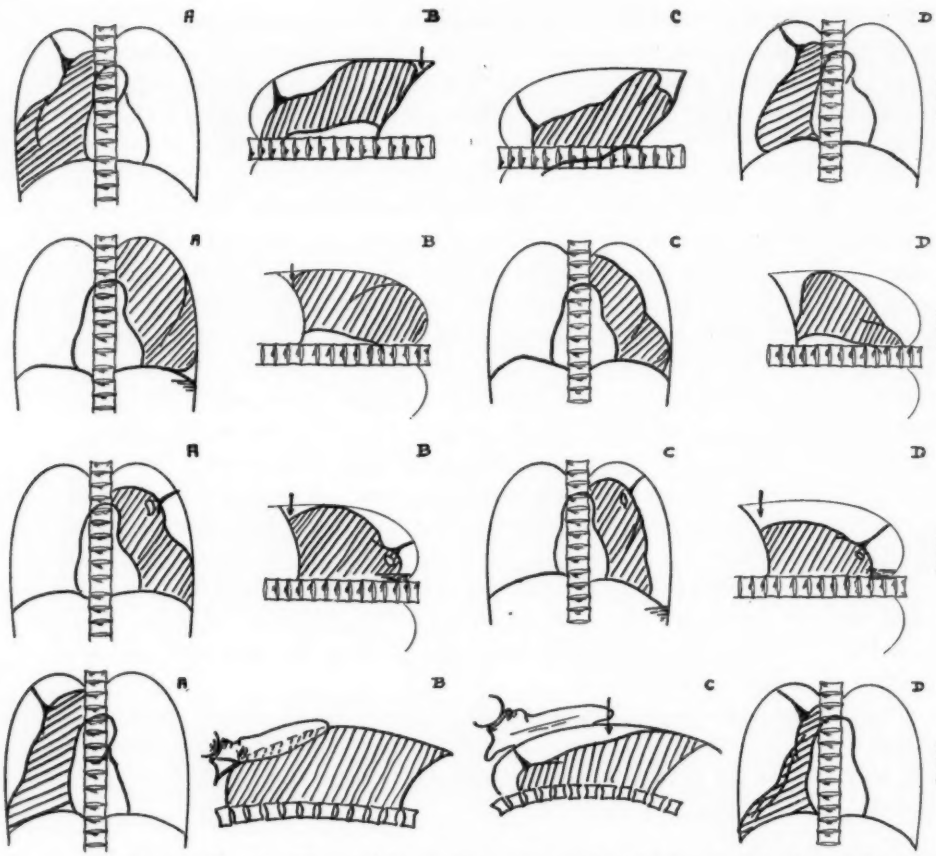



FIG. 11 A, B, C, D

FIG. 12 A, B, C, D

FIG. 13 A, B, C, D

FIG. 14 A, B, C, D

FIG. 11. Case 1. The upright tracings are ventral projections and the lateral decubitus studies are dorsal projections. In A and B partial adherence of the parietal and visceral pleurae is demonstrated. The pneumothorax needle was introduced into the pneumothorax pocket at the costophrenic angle under fluoroscopic guidance (see arrow in B) and the treatment was successfully given. The lung did not entirely separate from the chest-wall as is noted in (C). When the patient was studied in the upright posture, immediately after the treatment, (D) the lung was seen to tear away from the chest-wall. This case illustrates the presence of fibrinous adhesions between the two pleural parietes and how readily these adhesions may be separated if treatment can be continued and the adhesions are not allowed to form into fibrous bands.

FIG. 12. Case 2. The upright tracings are ventral projections and the lateral decubitus studies are dorsal projections. The costophrenic pneumothorax pocket is demonstrated in diagrams A & B. The pneumothorax needle was introduced into the costophrenic pocket under fluoroscopic guidance (see fig. 23), and the resulting collapse is shown in C & D.

FIG. 13. Case 3. The upright tracings are ventral projections; the horizontal diagrams are dorsal projections. In the right lateral decubitus (B) the small costophrenic pocket of pneumothorax is seen and the adherence of part of the lung to the thoracic wall is demonstrated. The pneumothorax needle was introduced into the costophrenic pneumothorax pocket in-

*Case 5:* (J. B.) This patient has been under artificial pneumothorax treatment since November, 1934. No difficulty was encountered during the administration of refills until June, 1935 when the fluoroscopic tracing in upright posture showed a very thin line of radiolucency along the axillary line representing the pneumothorax. At the apex the lung was adherent. In spite of this fluoroscopic appearance the operator made several chest punctures and was unable to find the pneumothorax space. The patient was then referred to the fluoroscopic pneumothorax clinic for study.

Preliminary fluoroscopy confirmed the original upright tracing. The study in right lateral decubitus, however, revealed a large pneumothorax space at the costophrenic angle. This site was chosen for the needle puncture and under fluoroscopic guidance the treatment was successfully given. Since then the patient has been receiving weekly treatments without difficulty and now has a satisfactory collapse. A more recent study shows the formation of band adhesions at the apex from what was previously an extensive apical adhesive pleuritis. (See figures 15A, B, C, D, E, F.)

*Case 6:* (L. B.) This patient had been under treatment for three months and had responded well to collapse therapy. The fluoroscopic tracing in upright posture showed a partial collapse of the lower lobe and no suspicion was entertained that difficulty might be encountered in giving the treatment.

The operator attempted to give the refill at the usual site, fifth interspace in the midaxillary line, but was unable to locate the pneumothorax. The patient was immediately referred to the fluoroscopic pneumothorax clinic. The following observations explained the operator's difficulty in giving the treatment. In the upright position the left lung was partially collapsed and at the caudal border of the upper lobe in the anterior axillary line adhesions were found extending to the chest-wall at the level of the axilla. The lower lobe did not appear to be in contact with the chest-wall in the axillary line. The right lateral decubitus, however, showed that the portion of the lower lobe adjacent to the adherent part of the upper lobe was in contact with the chest-wall and apparently the operator's needle struck this region. By rotating the

---

dicated by the arrow in B, and the resulting satisfactory collapse is shown in C & D. This case demonstrates the presence of fibrinous adhesions and again we see how easily they may be separated. Note also how easily the adherent lung could be injured if the pneumothorax needle was introduced into the chest at the point where the lung is adherent.

FIG. 14. Case 4. The upright tracings are ventral projections; the others are dorsal projections. In spite of the roentgen appearance of the chest in the upright posture (A) difficulty was encountered. In the left lateral decubitus left anterior oblique position (B) no pneumothorax was seen; in the right anterior oblique (C), however, a large pneumothorax was found, indicating that the lung was expanded along the ventral chest-wall and the pneumothorax was dorsal. Under fluoroscopic guidance the treatment was successfully administered through the fifth interspace in the posterior axillary line (arrow in C).

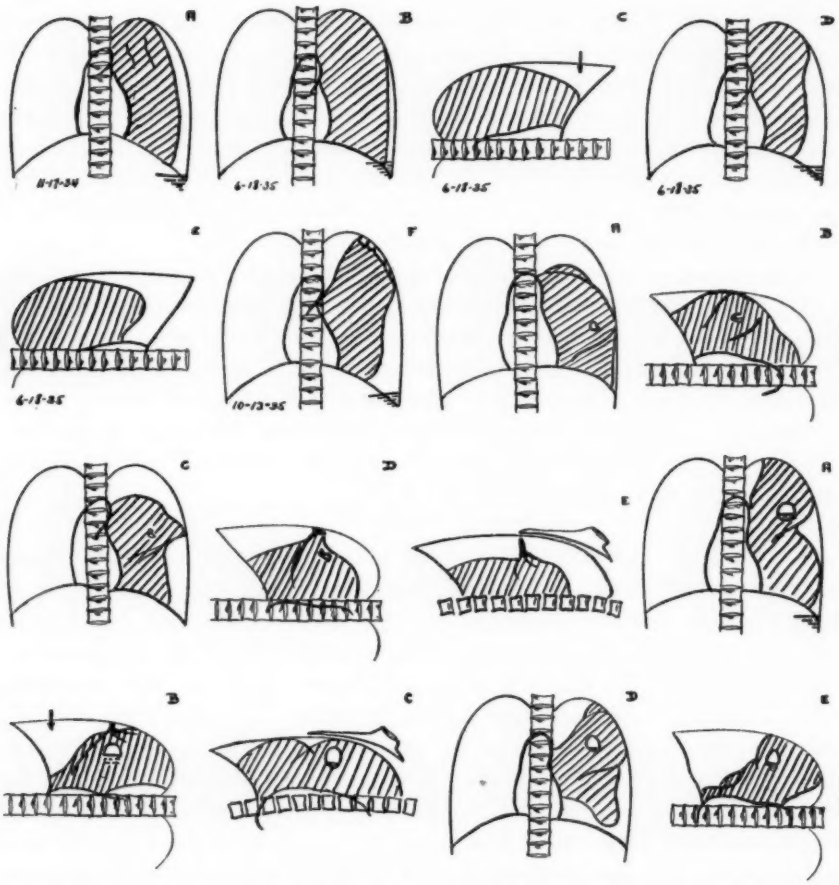


FIG. 15 A, B, C, D

FIG. 15, E, F

FIG. 16 A, B

FIG. 16 C, D, E

FIG. 17 A

FIG. 17 B, C, D, E

FIG. 15. Case 5. All the tracings are ventral projections. Diagram B demonstrates the pneumothorax at the time several punctures were made without success in locating the pneumothorax. The lateral decubitus study (C) revealed a large pocket of gas at the costophrenic sulcus. Under fluoroscopic guidance the needle was introduced at this point and the treatment was successfully given (arrow in C). The resulting collapse is shown in diagrams D & E. In diagram F the appearance of the chest is shown several months later and demonstrates how under continued pneumothorax treatment the extensive and adherent pleuritis at the apex separates and forms band adhesions.

FIG. 16. Case 6. The upright tracings are ventral projections while the horizontal tracings are dorsal projections. The diagram B demonstrates the adherent lung along the midaxillary line, and the cause for the unsuccessful attempt in locating the pneumothorax through the usual site, fifth interspace in the midaxillary line. The left and right anterior oblique positions demonstrated that the lung was reëxpanded and adherent to the anterior chest-wall to the level of the midaxillary line. The needle introduced in this region struck the adherent lung. Under fluoroscopic guidance the needle was then introduced through the eighth interspace in the posterior axillary line and the treatment was successfully given.

patient from a right anterior oblique to a left anterior oblique position it was determined that the left lower lobe had expanded along the ventral chest-wall to the level of the midaxillary line in the sagittal plane and that the pneumothorax was confined to the dorsal third of the left chest.

The patient was treated under fluoroscopic guidance through the eighth interspace in the posterior axillary line and since then the posterior axillary or midscapular sites have offered no difficulty in giving the refill. (See figures 16A, B, C, D, E.)

*Case 7:* (M. B.) This patient had been under artificial pneumothorax treatment for several years and no difficulty had ever been encountered in giving refills through the midscapular line. Because of difficulty in administering the treatment through the usual site, the patient was referred for special fluoroscopic study.

The upright position revealed a partial collapse of both lobes of the left lung. The upper lobe was found adherent from the apex to the level of the axilla. The lower lobe was partially collapsed and did not appear to be adherent to the chest-wall. The right lateral decubitus, left anterior oblique position (120°) (figure 17C), demonstrated the important fact that the lower lobe was in contact with the chest-wall. Two pneumothorax pockets were noted; one at the costophrenic angle and the other between the two lobes at the level of the axilla. When the patient was rotated to the true lateral decubitus (90°) (figure 17B), and to a right anterior oblique lateral decubitus (60°) a large pneumothorax was seen in the caudal half of the left chest. These observations demonstrated that the lower lobe was partially collapsed and was adherent along the dorsal chest-wall to the level of the posterior axillary line. Hence, when the needle was introduced through the midscapular line, it met lung tissue. The treatment was given in the anterior axillary line through the fourth interspace and no difficulty was experienced. Since then the patient has been treated successfully through this approach without the use of direct fluoroscopic guidance. (See figures 17A, B, C, D, E.)

*Case 8:* (F. S.) This patient had been attending the Eagleville Dispensary Clinic for several months and had always been comparatively easy to inflate. On November 8, 1935, the needle was introduced at the usual site (sixth inter-

---

FIG. 17. Case 7. The upright tracings are ventral projections while the horizontal diagrams are dorsal projections. Diagrams B & C demonstrate the important fact that the ventral portion of the lower lobe is partially collapsed and the lobe is adherent along the dorsal chest-wall to the level of the posterior axillary line. This explains the difficulty encountered when the needle was introduced through the usual midaxillary site. The treatment was successfully given through the fourth interspace in the anterior axillary line under fluoroscopic guidance.

space in posterior scapular line), but the operator was unable to locate the pneumothorax. No further attempts were made and the patient was referred to the fluoroscopic clinic.

Fluoroscopy in the upright position on November 12, 1935 revealed a partial collapse of the left lung and the presence of adhesions at the apex and at the level of the axilla (figure 18A). The left lower lobe was found expanded and in contact with the chest-wall in the axillary line, except at the costophrenic angle where a small pocket of pneumothorax was noted. In the right lateral decubitus (figure 18B) these findings were corroborated and it was noted that by rotating the patient to a left anterior oblique (120°) right lateral decubitus position the costophrenic pneumothorax pocket was increased. These observations explained the difficulty in administering the refill to this patient. The left lower lobe had reëxpanded and was adherent to the dorsal chest-wall. The needle when introduced in this region did not enter the pneumothorax but impinged against the expanded lung.

Under fluoroscopic guidance the needle was introduced into the pneumothorax pocket at the costophrenic angle (figure 24) without the slightest difficulty and the refill was successfully administered. Since then the refills have been continued without fluoroscopic aid. (See figures 18A, B, C, D, E and figure 24.)

*Case 9:* (H. F.) This patient had been under artificial pneumothorax treatment for one year and a very satisfactory collapse had always been maintained with ease. On November 5, 1935, in spite of a partial collapse as shown by the fluoroscopic tracing (figure 19B), the operator failed to enter the pleural cavity and blood spitting resulted. Only one attempt was made and the patient was referred for fluoroscopic study.

Fluoroscopic tracings and the roentgenogram in the upright position revealed a partial collapse of the right lung. At the level of the fifth rib in the midaxillary line, the site of usual needle puncture, the lung was found approximating the chest-wall. In the right lateral decubitus and in the right anterior oblique lateral decubitus positions (figures 19C and D), the lung was found adherent to the chest-wall and at the costophrenic angle a small pneumothorax pocket was visualized.

The needle was introduced into this pneumothorax pocket under fluoroscopic guidance and a very satisfactory collapse of the entire lung was obtained. During fluoroscopy the adherent lung was observed to peel away slowly from the chest-wall, indicating the presence of fibrinous adhesions between the parietal and visceral pleurae. Since then the patient has been successfully treated in the regular pneumothorax clinic. (See figures 19A, B, C, D, E, F.)

*Case 10:* (I. G.) This patient had artificial pneumothorax treatment on the left side for 6 years; two years ago it was discontinued. In September, 1933

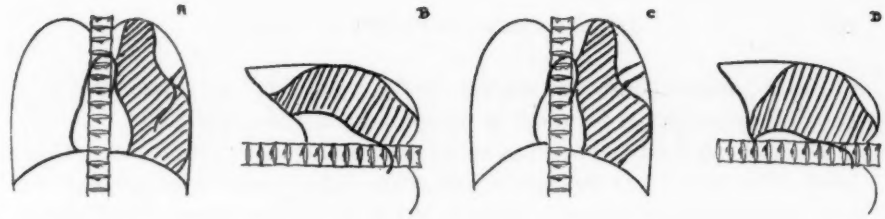



FIG. 18
A, B, C, D

FIG. 18 E

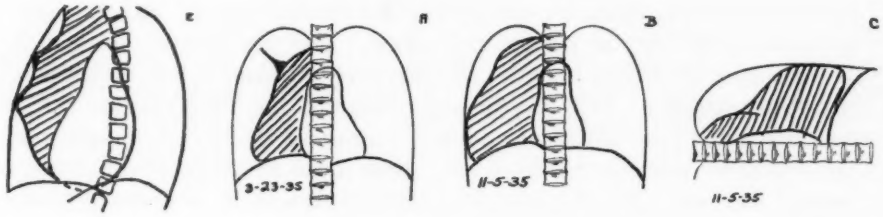



FIG. 19
A, B, C

FIG. 19
D, E, F

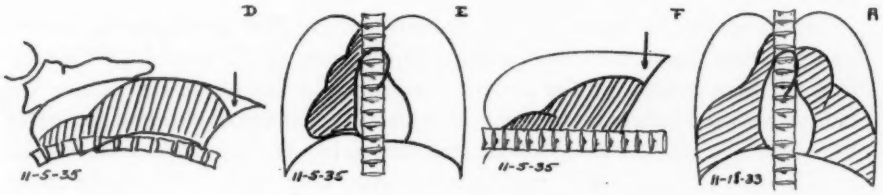



FIG. 20 A

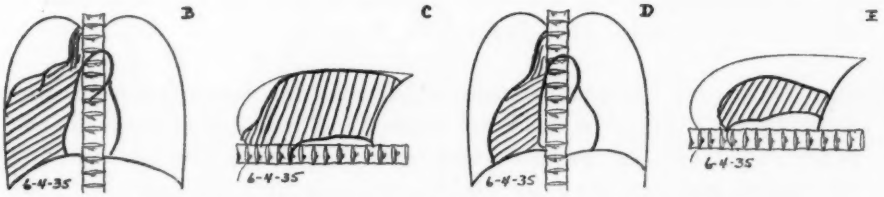



FIG. 20
B, C, D, E

FIG. 18. Case 8. A & C are ventral projections; B & D are dorsal projections and E is a right anterior oblique 45° dorsal projection. Diagrams A & B demonstrate the adherent lung along the axillary line. Pneumothorax is seen at the apex and at the costophrenic angle. The difficulty in locating the pneumothorax was due to introducing the needle into the area of obliterated pleural space. Under fluoroscopic guidance the needle was introduced into the costophrenic pocket and the refill was successfully given. C, D & E show the appearance of the left chest after treatment. (See fig. 24.)

FIG. 19. Case 9. The upright tracings are ventral projections while the horizontal diagrams are dorsal projections. In spite of the fluoroscopic appearance as is shown in B the pneumothorax was not located and blood spitting followed the attempt at refill. The left lateral decubitus study (C & D) showed that the lung had reëxpanded and had become adherent to the chest-wall. Under fluoroscopic guidance the pneumothorax needle was introduced into the costophrenic pneumothorax pocket and a successful treatment was carried out (E & F). During fluoroscopy the adherent lung was observed to peel away slowly from the chest-wall, indicating the presence of fibrinous adhesions.

FIG. 20. Case 10. A, B & D are ventral projections; C & E are dorsal projections. A shows appearance of bilateral collapse on November 18, 1933. Diagrams B & C demonstrate the reëxpanded and adherent lung—the reason for the encountered difficulty. Under fluoroscopic guidance the pneumothorax needle was introduced into the costophrenic pocket and the treatment was successfully given as is shown by diagrams D & E. Here again we observe the presence of fibrinous adhesions.

artificial pneumothorax was started on the right side. In June, 1935 difficulty was experienced for the first time in administering the refill.

Fluoroscopic study revealed an apical pneumothorax pocket extending to the level of the axilla. In the caudal half of the right chest the lung was in contact with the thoracic cage. The left lateral decubitus demonstrated the adherence of the lung along the axillary line and the presence of a minimal pneumothorax pocket at the costophrenic angle. This pocket was the smallest we have ever attempted to enter; comparatively speaking it was no larger in size than a quarter. With the utmost precaution the pneumothorax needle was introduced into this space and under continual fluoroscopic observation the treatment was successfully given. Here again fibrinous adhesions were present and accounted for the difficulty experienced in administering the treatment.

In this patient, on two occasions, we had observed that the diaphragm during its excursions would come in contact with the point of the needle. Following each of these treatments the patient complained of diaphragmatic pain. We believe that the pain was the result of injury to the diaphragm when the latter impinged against the point of the needle during the administration of the treatment. It was found necessary to give only three treatments under fluoroscopic guidance and since, the patient has been receiving treatment in the regular refill clinic. (See figures 20A, B, C, D.)

*Case 11:* (F. L.) This patient had artificial pneumothorax treatment since April, 1934. His collapse was never marked and limited to the cephalic half of the right lung. The pneumothorax needle had always been introduced at the highest point in the axilla and haemoptysis frequently occurred. On several occasions three attempts were necessary to locate the pneumothorax. For these reasons the patient was referred for special fluoroscopic study. The left lateral decubitus position revealed that the caudal two-thirds of the right lung had expanded and were adherent to the dorsal chest-wall, and the pneumothorax was confined to the apex. The left lateral decubitus, right anterior oblique (figure 21C) showed a fairly large pneumothorax pocket along the dorsum of the chest. Because of the greater thickness of the soft tissues in the posterior axillary line and the presence of the overlying scapula, the paravertebral region was chosen as the more satisfactory site for the needle insertion. The needle was readily introduced through the fifth interspace paravertebrally (figure 21C arrow, and figure 25) and the treatment was successfully carried out. Since then this has been the position of choice for the needle puncture and the treatments have been given without difficulty in the regular clinic.

For treatment in this position the patient lies obliquely (45°) resting on the unaffected side with arm abducted (180°) and the anterolateral chest-wall

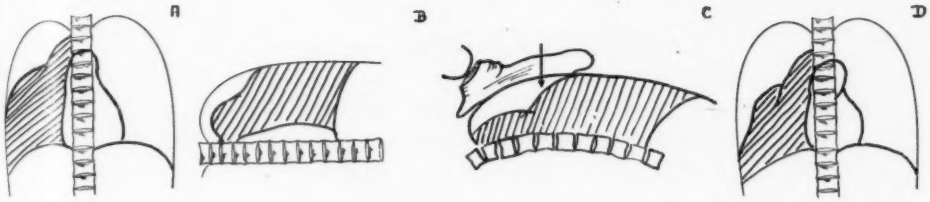



FIG. 21
A, B, C, D

FIG. 21 E

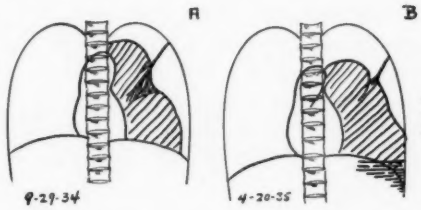



FIG. 22
A, B

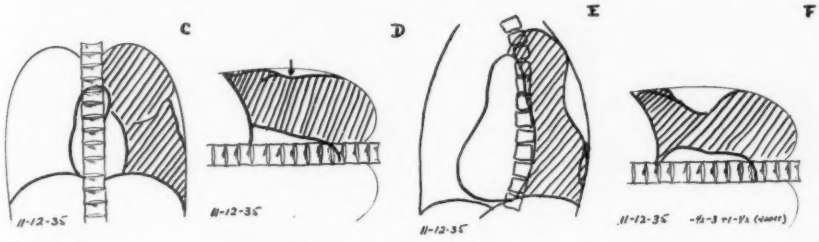



FIG. 22
C, D, E, F

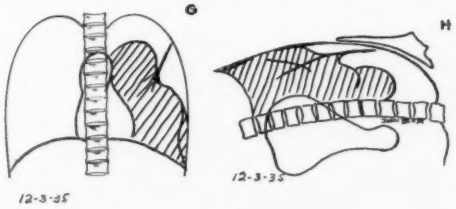



FIG. 22
G, H

FIG. 21. Case 11. The upright tracings are ventral projections and the horizontal diagrams are dorsal projections. Both the upright (A) and the lateral decubitus (B) diagrams show the right lung expanded and adherent to the chest-wall. This finding accounts for the difficulty in giving refills and also for the blood spitting sequelae. The left lateral decubitus, right anterior oblique (C) showed a fairly large pneumothorax pocket along the dorsum of the chest at the apex. Under fluoroscopic guidance the pneumothorax needle was introduced through the fifth interspace paravertebrally (C), and the treatment was given successfully as is shown by diagrams D & E. (See fig. 25.)

FIG. 22. Case 12. All the upright tracings are ventral projections; the horizontal tracings are dorsal projections; E is a right anterior oblique position, while H is a right lateral decubitus, left anterior oblique.

In October and November, 1935 the patient missed two treatments and on November 12, 1935 (C) the pneumothorax was not located. Only one attempt was made. Fluoroscopy revealed only a small pocket of air along the posterior axillary line at the level of the axilla (C & D). The pneumothorax needle was introduced into this pocket of air under fluoroscopic guidance and 400 cc. of air was introduced with the production of collapse as shown in E & F.

This patient represents that type of case which is ordinarily given up as hopeless for continuation of the artificial pneumothorax because of reëxpansion and obliteration. If detected early enough the obliterative phenomenon can be successfully combated as has been demonstrated by this case.

and the anterior axillary fold in apposition with the table. The approach through the dorsum of the chest can be made easy by displacing the scapula toward the axilla. This can be manoeuvred by abducting the arm (180°), flexing the elbow and then abducting and internally rotating the elbow. This manoeuvre brings the scapula laterad and somewhat cephalad, thus exposing a larger area of the dorsum of the chest. (See figures 21A, B, C, D, E.)

FIG. 23

FIG. 24

FIG. 23. Case 2. Roentgenogram made just before treatment showing the position and relation of the pneumothorax needle to the diaphragm and lung (see fig. 12).

FIG. 24. Case 8. Roentgenograms showing the position of the pneumothorax needle at the costophrenic angle and its proximity to the diaphragm and the expanded lung just prior to the refill. Note how small the pneumothorax pocket may be for a successful refill under fluoroscopic guidance.

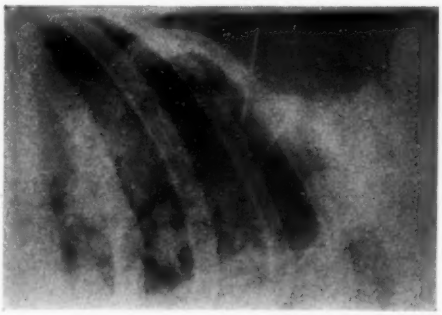


FIG. 25. Case 11. Roentgenogram made during the fluoroscopic administration of the refill. This is a left lateral decubitus, right anterior oblique, dorsal projection showing the needle *in situ* in the paravertebral region.

*Case 12:* (A. P.) Artificial pneumothorax was started on the left side in July, 1934. Beginning in July, 1935 the left side began to show evidence of not being able to retain a satisfactory pneumothorax for an interval greater than one week. The patient missed two treatments and on November 12, 1935 the needle was introduced at the usual site in the eighth interspace in the mid-

scapular line, but the pleural space could not be located. Because of our previous experiences no further attempts were made as we deemed this of sufficient importance to warrant special study.

Fluoroscopy revealed the fact that the entire left lung had reëxpanded except for a small pocket of air along the posterior axillary line at the level of the axilla. The lateral decubitus confirmed the presence of this pocket of air; it also demonstrated some air at the base near the costophrenic angle where there appeared to be several fine adhesions. Under fluoroscopic guidance we attempted to enter the costophrenic pocket but discovered that we were dealing with loculated pneumothorax collections. We decided, therefore, to try the pocket of gas higher up. Placing the patient in a left anterior oblique right lateral decubitus position (figure 22D) enabled us to visualize this pocket most satisfactorily. The actual site of needle puncture was selected by fluoroscopy and the pneumothorax was readily entered. Four hundred cubic centimetres of gas were given and only a localized collapse of the middle third of the left lung was obtained. The adhesions forming the loculi at the base were now definitely noted. Since then the patient has been receiving the refill treatment through this same site without fluoroscopic guidance and no difficulty has presented itself to date. In fact, the collapse has been reëstablished, the left upper lobe being well collapsed and the lower lobe being partially collapsed in spite of the costophrenic adhesions. The patient represents that group of difficult cases who are given up as hopeless because the obliterative phenomenon could not be successfully combated. (See figures 22A, B, C, D, E, F, G, H.)

### FLUOROSCOPIC OBSERVATIONS ON THE LUNG AND HEART DURING THE ADMINISTRATION OF ARTIFICIAL PNEUMOTHORAX

The induction of artificial pneumothorax under fluoroscopic guidance has given us the opportunity to observe the reactions of the thoracic viscera during the injection of the gas into the pleural cavity in initial and in refill cases.

In the initial cases it is not only interesting but amazing to watch the changes that occur in the appearance and in the position of the thoracic viscera when a pneumothorax is established. As the air is injected the lung adjacent to the point of the needle slowly peels away from the chest-wall and the separation of the visceral and the parietal pleurae is visible on the fluoroscopic screen. As the pressure in the pleural space increases the diaphragm becomes depressed and its contour assumes a straight line, such as is seen in the state of contraction. As a result the pneumothorax at the costophrenic angle becomes most prominent. In most cases the disease is limited to the upper lobes and this part

of the lung is the last to show any change. If the disease is centrally located so that there is very little or no pleural reaction this part collapses as readily as does the affected part of the lung. If, on the other hand, there is evidence of pleural reaction then the diseased lung collapses only where the two pleural parietes are not adherent.

In addition to these pulmonary changes a very definite shifting of the mediastinum to the unaffected side is noted. In some cases air is seen between the mediastinal structures and the lung.

A very interesting observation in two of our initial cases was the peculiar dancing or jumping movement of the heart, which might be characterized as a rhythmical swinging except that occasionally the heart actually appeared to jump. The onset of this dancing phenomenon occurred shortly after 100 to 200 cc. of air had been injected. A similar phenomenon was observed in the refill cases although it was not quite as striking. The heart commenced its dancing gyrations after 50 to 100 cc. of air had been injected. In some patients this peculiarity of the cardiac pulsation was more marked than in others. It was interesting to note, however, that in a majority of our patients, when they were examined fluoroscopically in the standing position five to ten minutes after the treatment, the pulsation of the heart had assumed a more normal character, even though there was still a certain amount of to and fro shifting of the entire heart with each beat. This peculiar movement had been described as the characteristic heart movement in pneumothorax. In most cases a slight increase in the heart rate was noted. The radial pulse usually increased from 4 to 10 beats during the administration of the treatment.

In the majority of the refill cases the injection of air first resulted in a partial depression (contraction) of the diaphragm followed by a gradual collapse of the lung; while in others the first changes were observed in the lung and the diaphragm did not become flattened until the pressure approached a neutral reading. In all of these cases pressure was exerted on the mediastinum and there was either a shifting of the entire mediastinum and its contents, or a bulging and sometimes even a herniation into the opposite pleural cavity, unless marked fixation of the mediastinum was present.

We observed small amounts of fluid at the costophrenic angle in practically all of our refill cases. The fluid was minimal in amount and its level was nearly always seen well below the dome of the diaphragm. The presence of this fluid was oftentimes more easily demon-

strated by fluoroscopy than on the X-ray films. In one of our initial cases we had the unusual opportunity to observe a small amount of fluid at the costophrenic angle immediately after the institution of the collapse.

It is practically impossible to describe verbally one's reactions when he observes all of these changes actually taking place before him on the fluoroscopic screen. Here, as in other fields, fluoroscopy has permitted us to observe and actually see what before we could only attempt to visualize in our imagination.

## SELECTIVE COLLAPSE

Our fluoroscopic and roentgenographic observations in the study of pneumothorax patients have shown that the characteristic appearance of the lung in "selective pneumothorax," or "selective collapse," oftentimes disappears when the patient is placed in lateral decubitus. In many of the cases the selectively collapsed lung would shift to the apex and the pneumothorax would be greatest at the costophrenic angle and along the axillary line. These observations suggested that "selective collapse" is either a shape which the lung assumes in the presence of pneumothorax in the upright position only, or that there is another underlying principle in this type of collapse.

The term "selective collapse" was coined to designate the type of collapse resulting in a compression of the diseased portion of the lung without seriously affecting the relatively healthy lung tissue. The advantage of this type of collapse was soon recognized and several theories were advanced from time to time in attempts to explain this phenomenon. Barlow (1), who first called attention to this type of collapse in 1922, suggested that the loss of the elastic tissue along with a natural tendency to collapse resulted in a gradual compression of the diseased portion of the lung. The loss of this normal structure prevented expansion of the diseased tissue; the surrounding normal tissue, however, would continue to expand almost to its normal limit.

Hennel and Stivelman (11) accepted this term with reservation and Bendove (2) suggested that the term might be misleading, although he subscribed to the idea that the greatest amount of collapse occurred in the diseased part of the lung. The following excerpt explains very definitely his concept of this phenomenon.

> There is no affinity of the diseased part for the air, neither is there a predilection in the air for the diseased part. It is simply a natural phenomenon explained

on physico-dynamic laws of displacement. The diseased, contracted part has either no respiratory movement at all or, if present, they are of very limited range, while the movements of the functioning lung are of a large amplitude and they drive the air out, or displace the air, which will naturally follow the line of least resistance, that is, the empty space produced by the contraction of the diseased portion.

Cutler (8, 9, 10) advanced Bendove's (2) conception a step further and considered the "expansile pulmonic force" the agent eventually responsible for the selective collapse. The expansile action of the healthy part of the treated lung by repeated expansion forced the imprisoned air in the pleural cavity toward the diseased part, thereby producing a gradual complete collapse which would then be indefinitely maintained. Henske and Ehlers (12) and Bronfin (4) did not believe that this constant hammering of the expansile force played any rôle in the development of a selective collapse.

The classical work of Coryllos (5, 6, 7) and his coworkers, on the pathological physiology in tuberculosis and on the gas exchange in the pulmonary tissues has explained many of the puzzling phenomena observed in tuberculosis. Coryllos (7) believes that the so called "selective collapse" of the lung already existed before the pneumothorax was induced so that the latter merely rendered the collapse apparent, the underlying principle being an atelectasis of the diseased lung. On the roentgenogram oftentimes the trachea and heart are seen displaced to the affected side and the diaphragm may be elevated. The intrapleural pressure in such cases was definitely lower and after the induction of pneumothorax these structures returned to their normal position. The intrapleural pressure, however, was maintained negative, thus precluding any argument that this resulted from compression.

We are in accord with this concept. In addition, however, we believe that quite frequently the selective collapse is formed or increases in extent after pneumothorax induction. In pulmonary tuberculosis bronchial lesions are commonly observed and such bronchi are easily obstructed either partially or completely. The presence of inflammatory reaction, allergic oedema, granulations, scar tissue and accumulation of secretions in the bronchus will aid in the production of an occlusion of the bronchus. By virtue of a pneumothorax or increase of the intrapleural pressure the collapse or occlusion of the diseased bronchi is readily accomplished. Thus an atelectasis of part of the diseased lung

communicating with such a bronchus is produced and a so called "selective collapse" is obtained.

The position studies have shown that the entire lung changes somewhat in shape and in position when the patient is placed in the lateral decubitus. The area of atelectatic diseased tissue remains unchanged, but the remaining portion of the lung appears to be more collapsed then when viewed in the upright position. The explanation is a purely mechanical one. The normal lung is attached at the hilum and the parenchyma of the lung is expanded by the negative intrapleural pressure to fill the entire pleural space. After pneumothorax, however, the lung is partially collapsed, the intrapleural pressure is less negative, and if the visceral and parietal layers of the pleura are not adherent, the now smaller lung is permitted a limited amount of shifting within the pleural space. The mobility of the mediastinum and diaphragm are other factors exerting some influence on the position of the pneumothorax lung in the vertical and lateral decubitus positions.

## SUMMARY AND CONCLUSIONS

We have made position studies in 146 individual pneumothorax patients and have administered 86 individual pneumothorax treatments under fluoroscopic guidance; seventy-four treatments were performed with the aid of an ordinary upright fluoroscope and twelve with the guidance of a biplane fluoroscope. The ordinary upright fluoroscope proved the more satisfactory for our purpose.

The most glaring error in the present method of pneumothorax study is the fact that the fluoroscopic examination is usually made in the upright position while the treatment is administered in the lateral decubitus. Our studies on the pneumothorax patient in the lateral decubitus and upright positions have shown that definite changes in the position of the collapsed lung occur when the patient is studied in the lateral decubitus. The cause of difficulty encountered in the administration of the refill treatment can be found and oftentimes easily remedied. In the relatively easy cases this procedure is acceptable; however, the difficult cases should always be studied in the lateral decubitus in an effort to find the cause of the difficulty.

The administration of artificial pneumothorax under fluoroscopic guidance is not a routine procedure and should be reserved only for the occasional difficult pneumothorax. We consider the following indications as deserving the lateral decubitus fluoroscopic study to

determine whether fluoroscopic guidance is needed during the administration of the refill:

(*1*) Inability to find pleural space
(*2*) The presence of air loculi
(*3*) The presence of adhesions at site of needle puncture
(*4*) All cases of blood spitting after treatment
(*5*) Patients who have missed treatment and have lost collapse
(*6*) In cases where pneumothorax is beginning to obliterate
(*7*) In any case in which treatment is hazardous and might be given with greater ease through another site

In a majority of the cases fluoroscopic guidance is unnecessary as the fluoroscopist, after studying the patient in the lateral decubitus position, is able to explain the cause of difficulty, advise how it may be avoided and indicate the most suitable site for the insertion of the needle without fluoroscopic guidance in the regular clinic.

Twelve cases are presented demonstrating some of the roentgenological findings which are or can be the cause for difficulty encountered in the administration of the treatment and how the lateral decubitus study and fluoroscopic guidance during administration of treatment successfully combated these difficulties.

The formation and presence of fibrinous adhesions in pneumothorax cases is demonstrated roentgenologically; their complications and method of treatment is discussed.

One of the most gratifying results was obtained in the reëstablishment of a pneumothorax in a patient who had reëxpanded and partially obliterated.

Fluoroscopic observations on the behavior of the thoracic viscera during the induction of artificial pneumothorax and during administration of refill treatments are presented.

Literature on so called "selective pneumothorax" is reviewed and its mechanism of production is explained on a pathological and physiological basis. We believe that atelectasis plus changes in the shape and position of the lung as a result of changes in intrapleural pressure are responsible for the picture entity described as "selective pneumothorax."

These fluoroscopic studies and observations have given us not only a better understanding of the difficulties one may encounter in the treatment of tuberculosis with artificial pneumothorax but also of how

we can successfully cope with these difficult situations. All guess work has been replaced by direct observation and visual guidance.

## REFERENCES

(1) Barlow, N., and Kramer, D.: Selective collapse under partial pneumothorax, Amer. Rev. Tuberc., 1922, *6*, 75.

(2) Bendove, R. A.: The classification of artificial pneumothorax and the clinical value of the several types, Ibid., 1925, *10*, 540.

(3) Blady, J., and Cohen, L.: Administration of artificial pneumothorax under fluoroscopic guidance, Radiol., 1935, *25*, 1.

(4) Bronfin, D. D.: Discussion of paper by J. W. Cutler, Natl. Tuberc. Assn. Tr., 1930, *26*, 158.

(5) Coryllos, P. N.: The importance of atelectasis in pulmonary tuberculosis, Amer. Rev. Tuberc., 1933, *28*, 1.

(6) Coryllos, P. N.: Thoracoplasty versus pneumothorax, Jour. Thoracic Surg., 1934, *4*, 30.

(7) Coryllos, P. N.: Pathologic physiology of the tuberculous lung in clinical tuberculosis, vol. 1, chap. v, A-151 to A-199, Edited by Benjamin Goldberg, F. A. Davis, Philadelphia, 1935.

(8) Cutler, J. W.: An improved technic for selective pneumothorax, Natl. Tuberc. Assn. Tr., 1930, *26*, 155.

(9) Cutler, J. W.: An improved technic for selective pneumothorax, Amer. Rev. Tuberc., 1930, *22*, 292.

(10) Cutler, J. W.: Clinical types of therapeutic pneumothorax and their significance, Jour. Amer. Med. Assn., 1934, *103*, 81.

(11) Hennell, H., and Stivelman, B. P.: So called selective collapse in artificial pneumothorax, Amer. Rev. Tuberc., 1923, *7*, 291.

(12) Henske, A. C., and Ehlers, C. W.: Selective pneumothorax, Jour. Missouri Med. Assn., 1931, *28*, 371.

(13) Gwerder, J.: Some observations on low tension pneumothorax, Tubercle, 1922, *4*, 13.

# THE EFFECT OF AGE ON THE TOTAL PULMONARY CAPACITY AND ITS SUBDIVISIONS[1]

NOLAN L. KALTREIDER, W. W. FRAY AND H. VAN ZILE HYDE

The effect of age on the vital capacity has been studied in great detail, but little is known concerning the influence of degenerative changes on the other subdivisions of the pulmonary capacity and on the shape, size and expansion of the chest. Since alterations in these anatomical measurements can be used as an index to respiratory efficiency in cases of chronic cardiorespiratory disorders, accurate standards should be obtained for normal individuals of all age groups. Hurtado *et al.* (1, 2) studied a group of young men and found definite limits of variation for the absolute and relative values of the total pulmonary capacity and its components, as well as a high correlation between the vital capacity and the "radiological chest volume." It seems probable that age influences not only the vital capacity but also other subdivisions of the pulmonary capacity. If this be true, the same formula for the prediction of the normal capacity cannot be applied to individuals of different age groups. This communication concerns the measurements of the capacity of the lungs and the expansion of the chest in normal men of the fifth and sixth decades.

## METHODS

The procedures employed in this investigation are similar to those described by Hurtado and Boller (1) and Hurtado and Fray (2). The mid capacity (functional residual air, subtidal volume or normal capacity) was determined by the oxygen dilution method of Christie (3). Duplicate determinations were made in each case. Corrections were made for the temperature (37°C.) and complete saturation with water vapor.

In addition to recording the complementary and reserve air separately, the vital capacity was measured by the ordinary vital capacity spirometer. Three determinations were made by each method, the highest

[1] From the Department of Medicine, School of Medicine and Dentistry, University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

value being accepted as the true one. All measurements were made with the subject in the recumbent position with a pillow to serve as a head rest. The nomenclature which we have adopted may be briefly summarized: *Residual air* is the volume of air remaining in the lungs after the greatest possible expiration. *Mid capacity* is the amount of air remaining in the lungs after a normal expiration. The terms "functional residual air," "normal capacity" and "subtidal volume" are synonymous with this term. *Vital capacity* is the amount of air expelled in the fullest possible expiration following the deepest possible inspiration. *Total capacity* is the sum of the vital capacity and the residual volume. *Complementary air* is the volume of air inspired from the position of mid capacity to that of maximum inflation. It includes the tidal volume. *Reserve air* is the amount of air expired from the mid capacity level to maximum possible deflation. The method of obtaining alveolar and tidal air has been described by Hurtado *et al.* (4).

The roentgenographic technique employed by Hurtado and Fray (2) has been modified to some extent, the general principles remaining unchanged. The appearance of the film has been improved by placing the brass filter near the X-ray tube rather than over the chest of the patient, eliminating the line on the film cast by the edge of the brass filter, figure 1. At the same time the operation of the filter has been made automatic by hinging the filter to a brass plate which slips into position beneath the tube on the under side of the tube carriage. This filter (0.5 mm. in thickness) is hinged back out of the way for the first exposure (maximum expiration) during which full exposure is desired. It is snapped into position for the second exposure (maximum inspiration) by a spring which is released by the pull of a solenoid, energized by the primary current of the first exposure. The tension on the spring is so adjusted that the first exposure is completed by the time the filter has been pulled into position. The filter is semicircular in shape, its filtering action being limited to the lower part of the chest. The purpose of the filter, it should be understood, is to prevent overexposure of the diaphragms during the second exposure (maximum inspiration) with resulting obliteration of their contours, a result which is certain to follow unless the exposure is greatly reduced. From the doubly exposed roentgenogram obtained in this manner, all the necessary linear and area measurements relating to chest size and expansion can be secured.

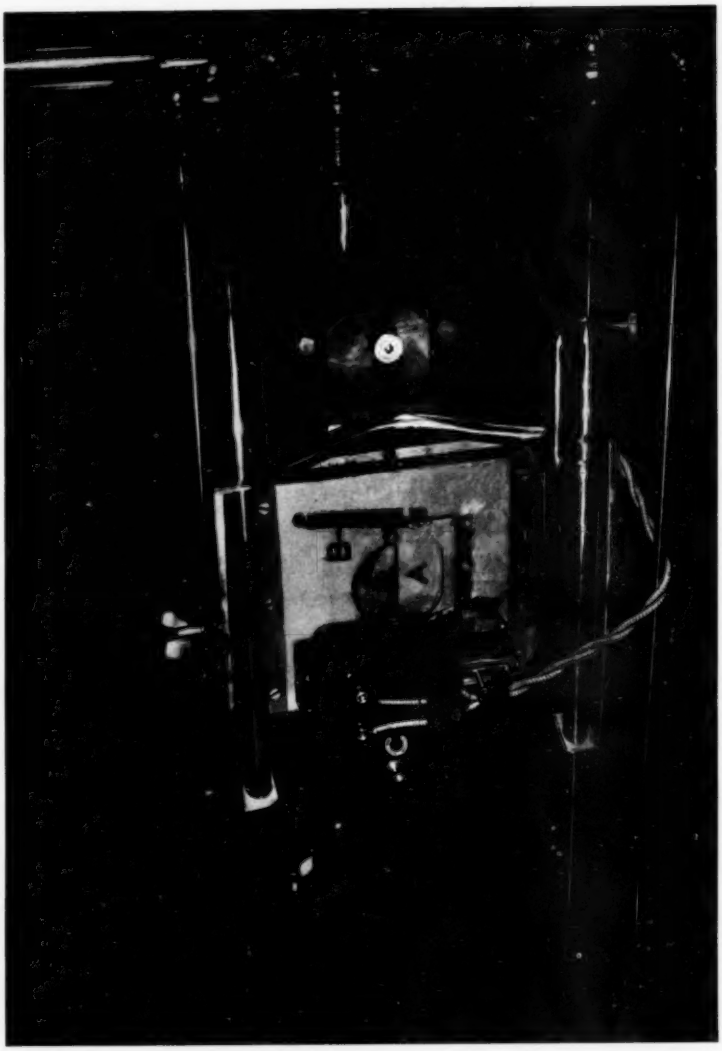



FIG. 1. View from below showing automatic shutter filter in position in the tube carriage beneath the X-ray tube. In this illustration the brass filter is shown in position for the second exposure, covering half of the portal through which the X-rays emerge. A: semi-circular filter. B: spring. C: solenoid.

### CALCULATION OF THE MID CAPACITY AND RESIDUAL AIR

In the past it has been our custom to calculate the volume of the mid capacity or the residual air by applying the formula given by Christie, that is

$$x = \frac{y(a - b)}{79.1 - y} - d - 80$$

where $x$ = mid capacity in cubic centimetres; $y$ = the percentage of nitrogen in the spirometer at the end of the rebreathing period; $a$ = oxygen in the spirometer at beginning of the experiment in cubic centimetres; $b$ = oxygen absorbed during the experiment in cubic centimetres and $d$ = dead space in cubic centimetres. Hurtado *et al.* (4) recently proposed a correction of this formula, in regard to the nitrogen excreted from the blood into the lung-spirometer system during the rebreathing period. The following quotation from their paper adequately explains the reason for such a correction.

> According to the above formula the nitrogen excretion has been corrected only in terms of gas volume added to the system during the rebreathing time, disregarding the fact that it has increased the nitrogen percentage found in the system at end of the experiment. The formula was developed by equating the volume of nitrogen in the system at the beginning of the experiment against the volume present at the end. By taking into account, in Christie's original equation, any volume of nitrogen (n) excreted into the spirometer-lung system and solving for x the following is obtained:
>
> $$x = \frac{y(a - b) - 100n}{79.1 - y} - d.$$
>
> Therefore, if 80 cubic centimeters are excreted during the time of the experiment we believe the formula should be:
>
> $$x = \frac{y(a - b) - 8000}{79.1 - y} - d.$$
>
> The application of the latter formula will give lower values for the residual air than those obtained from the former. Consequently the values given in this series of cases, as well as in the preceding ones for this subdivision of the pulmonary capacity are probably 100 to 150 cc. too high. Since this is a constant and probably not a very significant error, it does not invalidate our results, and permits comparative studies to be made with pathological cases.

In view of the fact that the second formula is presumably the more correct one and that the difference between the two is not a constant, we have recalculated the volume of the mid capacity of the 150 normal individuals thus far investigated by application of the second formula. The difference between the results of the two calculations varied from 100 to 260 cc. These variations are dependent upon the nitrogen percentage in the spirometer-lung system at the end of the rebreathing period, which in turn is dependent upon the amount of oxygen added to the spirometer, the length of the rebreathing period, the volume of the dead space, and whether the mid capacity or the residual air is determined directly. The first three factors have been kept constant during all of these experiments, that is, the oxygen (5,000 cc.) added to the spirometer, the dead space of the apparatus (2,600 cc.) and the rebreathing time (7 to 8 minutes). In the first two series (young men and women) the residual air was usually determined, while in the series herein reported the mid capacity was measured directly. In the series previously reported (1, 4) the average value for the mid capacity when calculated according to the formula proposed by Hurtado *et al.* was 160 cc. less than that when Christie's formula was applied. In the group of cases reported in this paper, in which the mid capacity was determined directly, the average difference for this volume was 220 cc. Similar changes will be found in the mean value for the total capacity and residual air. As a result of these alterations the relative values, ratios $\frac{\text{mid capacity}}{\text{total capacity}}$ and $\frac{\text{residual air}}{\text{total capacity}} \times 100$ will be slightly lower than those previously reported, namely 1.7 and 2.3 per cent respectively. The corrected values for the absolute and relative values of the 50 normal females and 50 normal males are presented in tables 1 and 2.

In all instances we have assumed that 80 cc. of nitrogen were excreted into the spirometer-lung system during the rebreathing period. The average value for the oxygen percentage in the spirometer at the end of the experiment was 54 per cent. This value is somewhat higher than that used by Christie (42 per cent), who suggested that a correction of 65 cc. of nitrogen be made.

Recently Lassen *et al.* (5) found that there was not an equal distribution of nitrogen throughout the spirometer-lung system. Most investigators who employed this method are cognizant of the fact that the concentration of nitrogen cannot be the same throughout the system, since the nitrogen percentage is changing continuously. But they

erroneously assumed that the nitrogen percentage in the lungs and hence in the expiratory tube was higher than in the spirometer by the same amount as the nitrogen percentage, when breathing atmospheric air, was higher in the expired air than in the inspired air. Lassen and his coworkers found that the nitrogen percentage in the lungs (alveolar air) was lower by 0.5 per cent than the nitrogen percentage in the spirom-

TABLE 1

*Pulmonary capacity in 50 healthy females (age limits, 18–34 years)*

| PULMONARY CAPACITY | MEAN | STANDARD DEVIATION | COEFFICIENT OF VARIATION | VARIATIONS |
|---|---|---|---|---|
| **Absolute values** | | | | |
| | *liters* | *liters* | *per cent* | *liters* |
| Total capacity | 4.24 ±0.05* | 0.57 ±0.04* | 13.5 | 3.20–6.18 |
| Vital capacity | 3.14 ±0.04 | 0.41 ±0.03 | 13.0 | 2.28–3.95 |
| Mid capacity | 1.82 ±0.04 | 0.39 ±0.03 | 21.6 | 1.15–3.10 |
| Complementary air | 2.42 ±0.03 | 0.36 ±0.02 | 14.8 | 1.70–3.32 |
| Reserve air | 0.73 ±0.02 | 0.19 ±0.01 | 25.8 | 0.28–1.42 |
| Residual air | 1.10 ±0.03 | 0.30 ±0.02 | 27.0 | 0.53–2.26 |
| **Relative values (total capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Vital capacity | 74.1 ±0.48 | 5.0 ±0.34 | 6.7 | 63.4–85.9 |
| Mid capacity | 43.0 ±0.53 | 5.6 ±0.38 | 13.0 | 27.5–52.3 |
| Complementary air | 57.0 ±0.55 | 5.8 ±0.39 | 10.2 | 47.7–72.5 |
| Reserve air | 17.0 ±0.34 | 3.6 ±0.24 | 21.2 | 6.1–27.1 |
| Residual air | 25.9 ±0.48 | 5.0 ±0.34 | 19.3 | 14.1–36.6 |
| **Relative values (vital capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Mid capacity | 58.5 ±1.01 | 10.6 ±0.72 | 18.1 | 35.0–79.1 |
| Complementary air | 77.1 ±0.72 | 7.6 ±0.51 | 9.8 | 64.1–92.2 |
| Reserve air | 22.9 ±0.43 | 4.6 ±0.31 | 20.1 | 7.8–35.9 |
| Residual air | 35.8 ±0.90 | 9.4 ±0.63 | 26.2 | 16.5–57.7 |

* Probable error

eter. In a series of 16 determinations of the mid capacity in 6 normal individuals, in contrast to their results, we found the average value for the alveolar nitrogen percentage at the end of the rebreathing period was higher by 0.14 per cent than that of the spirometer. The difference, however, is somewhat less than that between the nitrogen percentage of the alveolar air just before the rebreathing period and that of atmos-

pheric air, 79.1 per cent. Therefore, the average value for the mid capacity was 77 cc. (extremes of 23 and 190 cc.) lower when correction was made for the unequal distribution of nitrogen in the spirometer-lung system than when calculated according to the formula of Hurtado *et al.* The volume of the mid capacity varied from 1,850 to 3,250 cc. This difference is not nearly so great as that reported by Lassen *et al.* In

TABLE 2

*Pulmonary capacity in 50 healthy males (age limits, 18–30 years)*

| PULMONARY CAPACITY | MEAN | STANDARD DEVIATION | COEFFICIENT OF VARIATION | VARIATIONS |
|---|---|---|---|---|
| **Absolute values** | | | | |
| | *liters* | *liters* | *per cent* | *liters* |
| Total capacity | 5.97 ±0.08* | 0.81 ±0.06* | 13.6 | 4.25–7.68 |
| Vital capacity | 4.78 ±0.06 | 0.59 ±0.04 | 12.3 | 3.40–5.85 |
| Mid capacity | 2.18 ±0.05 | 0.50 ±0.03 | 22.9 | 0.96–3.09 |
| Complementary air | 3.79 ±0.05 | 0.52 ±0.04 | 13.7 | 2.41–4.93 |
| Reserve air | 0.98 ±0.02 | 0.26 ±0.02 | 26.5 | 0.26–1.58 |
| Residual air | 1.19 ±0.03 | 0.35 ±0.02 | 27.1 | 0.56–1.98 |
| **Relative values (total capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Vital capacity | 80.2 ±0.45 | 4.7 ±0.32 | 5.8 | 70.3–89.7 |
| Mid capacity | 36.2 ±0.52 | 5.4 ±0.36 | 14.9 | 19.0–46.9 |
| Complementary air | 63.9 ±0.52 | 5.5 ±0.37 | 8.6 | 53.1–81.0 |
| Reserve air | 16.8 ±0.56 | 5.9 ±0.40 | 35.1 | 5.2–31.4 |
| Residual air | 19.8 ±0.42 | 4.4 ±0.30 | 22.2 | 10.3–29.7 |
| **Relative values (vital capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Mid capacity | 45.8 ±0.81 | 8.5 ±0.57 | 18.5 | 22.1–66.7 |
| Complementary air | 79.4 ±0.50 | 5.2 ±0.35 | 6.5 | 63.1–94.1 |
| Reserve air | 20.6 ±0.52 | 5.4 ±0.36 | 26.2 | 5.9–36.9 |
| Residual air | 25.1 ±0.66 | 6.9 ±0.47 | 27.5 | 11.4–42.3 |

* Probable error

order to obtain samples of alveolar air the subject must be familiar with the experiment and close coöperation is necessary between the subject and experimenter. This makes it a rather impractical test, especially for patients with acute and chronic cardiorespiratory disorders. In many diseases, the reserve air is so small that it is practically impossible to collect consistent alveolar air samples. For this reason we feel that

the method herein used, although the values are slightly too high, is more applicable to the investigation of clinical problems than that suggested by Lassen *et al.*

## MATERIAL

Measurements of the total pulmonary capacity and its subdivisions were made in 50 normal men between the ages of 38 and 63 years. In addition two normal men of 67 and 76 years, not included in the average values, were examined. The physical characteristics of the subjects examined are presented in table 3. All the subjects were submitted to physical and roentgenographic examinations and only those individuals free from any discernible disease were included. Many subjects were

TABLE 3

*Physical characteristics of the subjects examined*

| | MEAN | STANDARD DEVIATION | COEFFICIENT OF VARIATION | VARIATIONS |
|---|---|---|---|---|
| | | | *per cent* | |
| Age, years | 48.2 ±0.61* | 6.4 ±0.43 | 13.4 | 38 – 63 |
| Body height, cm | 170.5 ±0.69 | 7.2 ±0.48 | 4.2 | 151.5–191.5 |
| Body weight, kgm | 70.8 ±1.15 | 12.1 ±0.81 | 17.0 | 49.2– 96.2 |
| Body surface area, $cm.^2$ | 182.1 ±1.60 | 16.7 ±1.13 | 9.2 | 143 –221 |
| Chest volume, liters (M.C.) | 10.4 ±0.17 | 1.8 ±0.12 | 17.3 | 6.7– 14.8 |
| Chest index, $\frac{\text{depth}}{\text{width}} \times 100$ | 74.1 ±0.46 | 4.8 ±0.32 | 6.5 | 64.3– 86.0 |

* Probable error

not accepted because of high arterial blood-pressure, arteriosclerotic heart disease, chronic bronchial infections, etc. Forty-two, or 84 per cent, of the individuals were machinists, painters, carpenters, etc. accustomed to moderate manual labor, while 8 or 16 per cent were professional men.

## NORMAL VALUES IN THE LITERATURE

Numerous studies have been made on the influence of age on the vital capacity. Bowen and Platt (6) and Lemon and Moersch (7) found little change until the sixth decade, following which there was a gradual decrease in the vital capacity until it reached 50 per cent of the normal value in the 85th year. The former investigators found that the greatest fall was between 50 and 60 years. Another group, Hutchinson

(8), Pratt (9) and Myers and Maeder (10) found that there was a gradual decrease in this capacity from the maximum values at the end of the third decade to 50–60 years, then a more rapid decline. Others, McKean (11), Cornett (12), and Wintrich (13), observed that the vital capacity remained practically the same until the 35th or 40th year, after which there was a gradual decrease until the 50th year, then a sharp decline. Piolti (14) studying 100 cases between the ages of 17 and 50 years observed a gradual fall after 25 to a maximum at 42 followed by a slight rise at that point and then a gradual decrease to 50 years. Myers and Cady (15), Levison (16) and Levy (17) studied a large group of older men and found that there was a gradual decline in the vital capacity from 60 to 94 years. Those who continued to be active showed less fall than those who retired from work (Myers and Cady). The consensus appears to be that the vital capacity is only slightly decreased from 40 to 50 years, following which there is a more rapid decline.

The other subdivisions of the total capacity have not been subjected to investigation in respect to the influence of age. In most instances individuals of all ages are presented together and in many cases the ages are not given, so that no conclusions can be drawn from the values presented by various observers.

## RESULTS

The results of the determinations of the total pulmonary capacity and its components in 50 healthy male subjects between the ages of 38 and 63 years are summarized in table 4.

*Absolute values:* The mean value for the *total capacity* was 5.37 $\pm$0.08 liters with a standard deviation of 0.84 $\pm$0.06 liter, giving a total variation around the mean of 31 per cent. The extremes were 3.62 and 7.61 liters.

There was an equally wide variation of 30 per cent about the mean value of 4.07 $\pm$0.06 liters for the *vital capacity*. The extreme values were 2.64 and 5.85 liters. The components of the vital capacity, the *complementary* and *reserve* volumes had mean values of 3.37 $\pm$0.05 and 0.69 $\pm$0.03 liters respectively. These subdivisions showed marked fluctuations particularly in the case of the reserve air, in which the total variation from the mean exceeded 90 per cent.

The extreme variations for the *mid capacity* were 1.09 and 3.05 liters, with a mean value of 2.00 $\pm$0.05 and a standard deviation of 0.50 $\pm$0.03 liters.

The fluctuations of the *residual air* were somewhat greater than those for the mid capacity. This was probably due to the marked variation in the reserve air. The mean value for this volume was 1.30 ±0.04 liters with a standard deviation of 0.41 ±0.03 liter and extremes of 0.54 and 2.29 liters.

TABLE 4

*Pulmonary capacity in 50 healthy males (age limits, 38–63 years)*

| PULMONARY CAPACITY | MEAN | STANDARD DEVIATION | COEFFICIENT OF VARIATION | VARIATIONS |
|---|---|---|---|---|
| **Absolute values** | | | | |
| | *liters* | *liters* | *per cent* | *liters* |
| Total capacity | 5.37 ±0.08* | 0.84 ±0.06* | 15.7 | 3.62–7.61 |
| Vital capacity | 4.07 ±0.06 | 0.62 ±0.04 | 15.2 | 2.64–5.85 |
| Mid capacity | 2.00 ±0.05 | 0.50 ±0.03 | 25.0 | 1.09–3.05 |
| Complementary air | 3.37 ±0.05 | 0.57 ±0.04 | 17.0 | 2.04–4.75 |
| Reserve air | 0.69 ±0.03 | 0.31 ±0.02 | 45.3 | 0.14–1.76 |
| Residual air | 1.30 ±0.04 | 0.41 ±0.03 | 31.4 | 0.54–2.29 |
| **Relative values (total capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Vital capacity | 75.5 ±0.52 | 5.58 ±0.38 | 7.2 | 62.4–86.8 |
| Mid capacity | 37.7 ±0.62 | 6.52 ±0.44 | 17.3 | 25.3–52.6 |
| Complementary air | 62.5 ±0.61 | 6.44 ±0.43 | 10.3 | 47.4–74.7 |
| Reserve air | 13.0 ±0.51 | 5.32 ±0.36 | 40.7 | 3.3–32.0 |
| Residual air | 24.5 ±0.53 | 5.58 ±0.38 | 22.8 | 13.2–37.6 |
| **Relative values (vital capacity = 100 per cent)** | | | | |
| | *per cent* | *per cent* | *per cent* | *per cent* |
| Mid capacity | 50.0 ±1.13 | 11.80 ±0.80 | 23.6 | 29.2–84.3 |
| Complementary air | 83.0 ±0.65 | 6.84 ±0.46 | 8.2 | 62.1–95.8 |
| Reserve air | 17.0 ±0.69 | 7.24 ±0.49 | 41.6 | 4.2–37.9 |
| Residual air | 33.6 ±0.95 | 9.96 ±0.67 | 29.7 | 15.2–60.3 |

* Probable error

The variations of the absolute values for the several capacities in this group of men were somewhat higher but in general corresponded fairly closely to those found in a group of younger men previously reported (1). There were, however, significant differences between the two groups. There was a significant decrease in the total capacity for the older men as compared with those in the third decade, namely, absolute difference, 0.60 ±0.11 liter and percentage difference, 10.0.

Likewise the vital capacity was smaller in the former than in the latter group, showing a significant absolute difference of 0.71 ±0.07 liter and a percentage difference of 14.9. The mid capacity was slightly lower and the residual air slightly higher in the men of the fifth decade and sixth decade than in the younger men. These differences, however, were insignificant. The volumes of the complementary and reserve air were significantly smaller in the former than in the latter group.

*Relative values:* As has been shown above the absolute values varied widely, but when they were expressed as percentage of the total capacity, the fluctuations were much less marked. The ratio $\frac{\text{vital capacity}}{\text{total capacity}} \times 100$ had a mean value of 75.5 ±0.52 per cent with a standard deviation of only 5.6 ±0.38 and a total variation of less than 15 per cent from the mean value. The ratio $\frac{\text{residul air}}{\text{total capacity}} \times 100$ showed corresponding fluctuations with extremes of 13.2 and 37.6 per cent.

The mean value for the ratio $\frac{\text{mid capacity}}{\text{total capacity}} \times 100$ was 37.7 ±0.62 per cent with a standard deviation of 6.5 ±0.44. The ratio $\frac{\text{complementary air}}{\text{total capacity}} \times 100$ had a mean value of 62.5 ±0.61 per cent with a total variation of 21 per cent from the mean value.

A similar constancy in the ratio $\frac{\text{vital capacity}}{\text{total capacity}} \times 100$ was observed in the group of younger men. The vital capacity constituted a smaller portion and the residual air a relatively larger part of the total capacity in this group of men than in the younger individuals. The change was significant and the absolute difference was 4.7 ±0.69.

The relationship between the total capacity and its subdivisions as expressed by the correlation coefficients is presented in table 5. High and significant correlations existed between the total, vital and mid capacities and the complementary and residual volumes.

### ALTERATIONS IN PULMONARY CAPACITY WITH BODY POSTURE

In order to ascertain the influence of posture on the pulmonary capacity in older men, determinations were made on 10 normal male subjects between the ages of 40 and 51 years in both the recumbent and sitting positions. Measurements were made after the subject was in the respective position for 20 minutes.

TABLE 5

*Correlations between the different subdivisions (age limits, 38–63 years)*

| CAPACITIES CORRELATED | CORRELATION COEFFICIENT |
|---|---|
| Total capacity and vital capacity | +0.8268 ±0.0302* |
| Total capacity and mid capacity | +0.7501 ±0.0417 |
| Total capacity and complementary air | +0.8084 ±0.0331 |
| Total capacity and reserve air | +0.5807 ±0.0632 |
| Total capacity and residual air | +0.7380 ±0.0434 |
| Vital capacity and mid capacity | +0.4749 ±0.0739 |
| Vital capacity and complementary air | +0.8289 ±0.0299 |
| Vital capacity and reserve air | +0.4208 ±0.0785 |
| Vital capacity and residual air | +0.2737 ±0.0883 |
| Mid capacity and reserve air | +0.6576 ±0.0541 |
| Mid capacity and residual air | +0.7949 ±0.0351 |
| Complementary air and mid capacity | +0.2484 ±0.0895 |
| Complementary air and reserve air | +0.0884 ±0.0947 |
| Complementary air and residual air | +0.4008 ±0.0801 |
| Residual air and reserve air | +0.0748 ±0.0950 |

* Probable error

TABLE 6

*Changes in pulmonary capacity according to posture (mean of 10 observations) (age limits, 40–51 years)*

| DETERMINATION | MEANS | | VARIATION | |
|---|---|---|---|---|
| | Sitting | Lying | | |
| | *liters* | *liters* | *per cent* | *liters* |
| Total capacity | 5.92 ±0.16* | 5.29 ±0.16* | −10.6 | 0.63 |
| Vital capacity | 4.30 ±0.14 | 4.11 ±0.15 | −4.4 | 0.19 |
| Mid capacity | 2.92 ±0.06 | 1.95 ±0.10 | −33.2 | 0.97 |
| Complementary air | 3.00 ±0.01 | 3.34 ±0.12 | +11.2 | 0.34 |
| Reserve air | 1.30 ±0.08 | 0.77 ±0.09 | −40.7 | 0.53 |
| Residual air | 1.62 ±0.09 | 1.18 ±0.07 | −27.2 | 0.44 |
| Relative values (total capacity = 100 per cent) | | | | |
| | *per cent* | *per cent* | | |
| Vital capacity | 72.7 ±1.31 | 77.7 ±1.08 | | |
| Mid capacity | 49.6 ±0.41 | 36.7 ±1.36 | | |
| Complementary air | 50.4 ±0.47 | 63.3 ±1.24 | | |
| Reserve air | 22.2 ±1.36 | 14.4 ±1.10 | | |
| Residual air | 27.3 ±1.40 | 22.3 ±1.13 | | |
| Relative values (vital capacity = 100 per cent) | | | | |
| | *per cent* | *per cent* | | |
| Mid capacity | 68.8 ±1.91 | 46.1 ±2.34 | | |
| Complementary air | 69.9 ±1.27 | 81.6 ±1.83 | | |
| Reserve air | 30.1 ±1.31 | 18.4 ±1.72 | | |
| Residual air | 38.7 ±2.68 | 29.3 ±2.00 | | |

* Probable error

When the subjects assumed the recumbent posture there was, as compared with the sitting position, a moderate reduction in the total capacity (10.6 per cent), a slight reduction in the vital capacity (4.4 per cent) and a more marked decrease in the mid capacity and residual air

TABLE 7

*Changes in size and expansion of the chest with body posture (from roentgenographic observations—mean of 10 cases)*

| MEASUREMENT | MEANS | | VARIATION | |
|---|---|---|---|---|
| | Sitting | Lying | | |
| | | | *per cent* | *units* |
| Height of diaphragm: | | | | |
| At maximum expiration: | | | | |
| Right, cm | 19.0 ± 0.28* | 17.8 ± 0.27 | −6.3 | 1.2 |
| Left, cm | 19.7 ± 0.39 | 19.1 ± 0.32 | −3.0 | 0.6 |
| At maximum inspiration: | | | | |
| Right, cm | 25.7 ± 0.39 | 23.1 ± 0.40 | −10.0 | 2.6 |
| Left, cm | 26.8 ± 0.36 | 25.2 ± 0.36 | −6.0 | 1.6 |
| Area of pulmonary fields: | | | | |
| At maximum expiration, $cm.^2$ | 442 ± 8.81 | 408 ± 8.43 | −7.7 | 34.0 |
| At maximum inspiration, $cm.^2$ | 700 ±16.19 | 642 ±12.32 | −8.3 | 58.0 |
| Excursion of diaphragm: | | | | |
| Total: | | | | |
| Right, cm | 6.8 ± 0.23 | 5.3 ± 0.32 | −22.1 | 1.5 |
| Left, cm | 7.0 ± 0.31 | 6.0 ± 0.28 | −14.3 | 1.0 |
| Expansion in chest width, total, cm. | 2.5 ± 0.14 | 3.1 ± 0.15 | +24.0 | 0.6 |
| Changes in area of pulmonary fields, total, $cm.^2$ | 259 ±12.05 | 234 ± 9.06 | −9.7 | 25.0 |
| Rib movement, degrees | 18.2 ± 1.07 | 19.2 ± 0.71 | +5.5 | 1.0 |
| $\frac{\text{Area at maximum expiration}}{\text{Area at maximum inspiration}} \times 100$, ratio | 63.3 ± 1.10 | 63.7 ± 1.03 | +0.6 | 0.4 |
| "Radiological chest volume": | | | | |
| Maximum expiration, liters | 9.4 ± 0.23 | 8.7 ± 0.17 | −7.4 | 0.7 |
| Maximum inspiration, liters | 16.9 ± 0.41 | 15.5 ± 0.31 | −8.3 | 1.4 |

* Probable error

(33.2 and 27.2 per cent respectively) (table 6). The only capacity which showed a change in the opposite direction was the complementary air.

The alterations in the absolute values on assuming the lying position are reflected in their relative values. The changes were slight for the ratio $\frac{\text{vital capacity}}{\text{total capacity}} \times 100$ but there were marked reductions in the

ratios $\frac{\text{mid capacity}}{\text{total capacity}} \times 100$ and the $\frac{\text{reserve air}}{\text{total capacity}} \times 100$. There was an equally large increase in the ratio $\frac{\text{complementary air}}{\text{total capacity}} \times 100$ on changing from sitting to recumbent posture.

The influence of posture on the shape, size and expansion of the chest is summarized in table 7.

The effect of posture on the alterations of the pulmonary capacity in this series is similar to that found in normal subjects of the third decade (18).

## RESPIRATORY DEAD SPACE

The alveolar air was collected and analyzed for its carbon dioxide and oxygen percentage in 42 of the subjects according to the method described previously (4). The mean value for the carbon dioxide tension of the alveolar was 39.2 ±0.38 with a standard deviation of 3.68 ±0.27 and extremes of 32.0 and 46.00 mm. of Hg. These values are in agreement with those of Haldane and Fitzgerald (19). For the oxygen tension of the alveolar air, the mean value was found to be 101.9 ±0.73 with extreme values of 86 and 115 mm. of Hg.

The respiratory dead space was calculated according to the Haldane-Priestley formula (20) from the tidal volume and the carbon dioxide percentages of the tidal and alveolar air. The measurements were made in the sitting position. The volume of the dead space had a mean value of 256 ±11.6 cc. corresponding to a mean tidal volume of .764 ±0.03 liter, with a mean respiratory rate and ventilation per minute of 15.0 ±0.3 and 10.5 ±0.3 liters respectively.

Considerable variations of the dead space have been found in this series. The standard deviation was 112 ±8.2 with a total variation of 87 per cent. However, the respiratory dead space showed a definite correlation with the tidal volume (figure 2), the correlation coefficient being +0.8836 ±0.0227 (figure 2). The correlation was linear as the correlation ratio was 0.933 giving an insignificant $\sqrt{n^2 - r^2}$ of 0.0890 ±0.0616.

It has been found in this series as shown by Haldane (21) that the variations in the volume of the dead space were independent of the respiratory rate. If a constant respiratory rate in the 42 cases is assumed, the standard deviation corresponding to the value of the dead space will be only slightly reduced, becoming 97.4 cc. instead of 111.5

or a reduction of 13 per cent. When a fixed tidal volume in all cases is assumed the corresponding standard deviation falls from 111.5 cc. to 52.2, or a reduction of 52.2 per cent. These results are in agreement

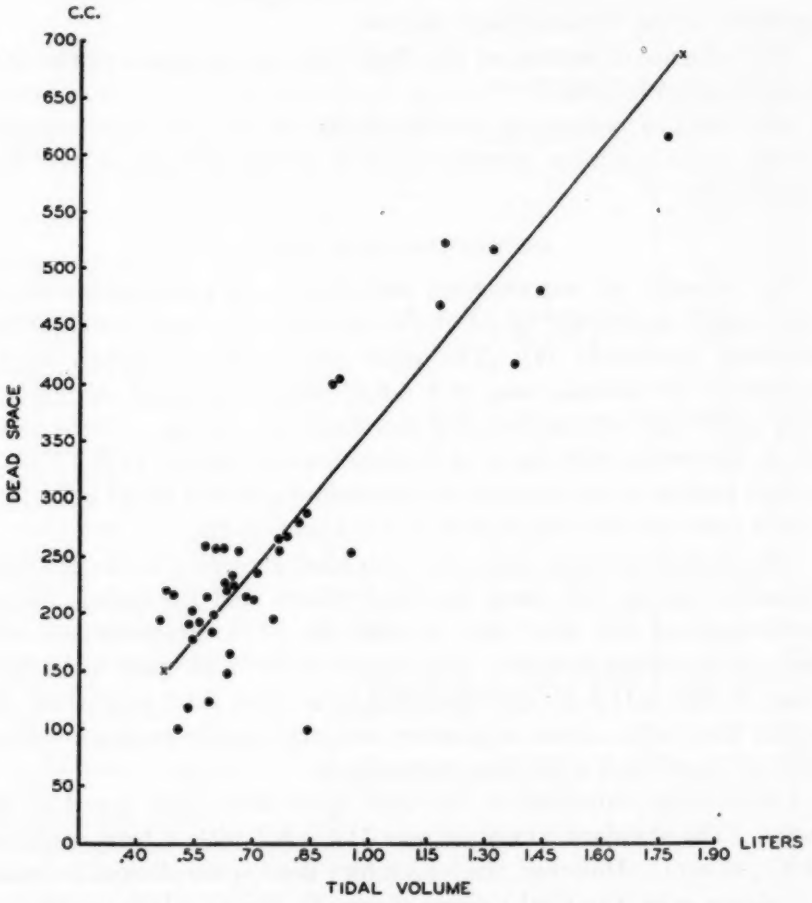



FIG. 2. Correlation between the tidal volume and the respiratory "dead space"

with those obtained by Hurtado *et al.* (4) in an investigation of 50 normal female subjects.

## CORRELATION OF PULMONARY CAPACITY WITH PHYSICAL AND ROENTGENOGRAPHIC MEASUREMENTS

The highest correlation in the series was between the total capacity and the "radiological chest volume" (the product of the area of the

pulmonary fields and the depth of the chest in the same respiratory position) at maximum inspiration. The correlation coefficient was +0.8497 ±0.0265 (figure 3). The next most significant correlation

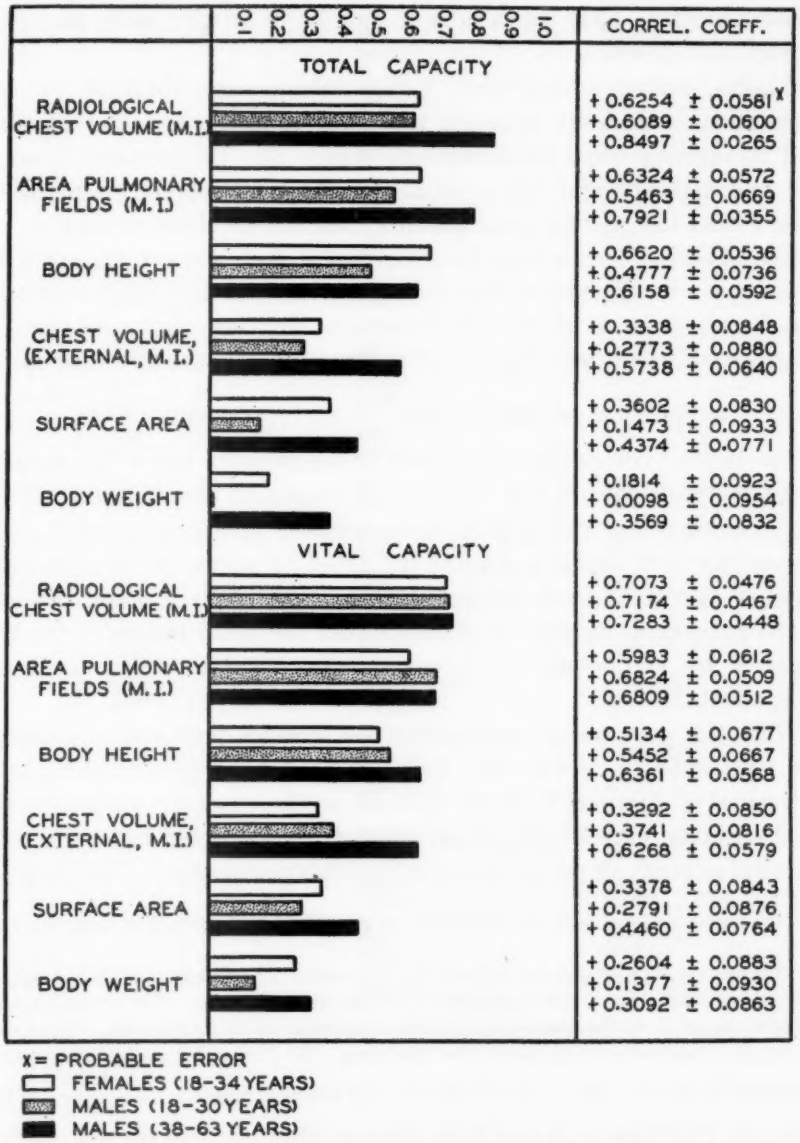



FIG. 3. Correlation between the pulmonary capacity and the physical and roentgenographic measurements.

was with the area of the pulmonary fields at maximum inspiration, where the coefficient was $+0.7921 \pm 0.0355$. There was a fairly high correlation between the total capacity and body height. Correlations between this capacity and the chest volume (calculated from external measurements), body surface area and body weight were all lower (figure 3).

Similar, although somewhat lower, values were obtained for the correlation coefficients between the vital capacity and the physical and roentgenographic measurements (figure 3). Correlations between the mid capacity and the residual air and the several measurements were rather low and in some instances statistically insignificant.

The observed correlations in this group of men in the fifth and sixth decades are in agreement with those previously found in normal male and female subjects of the third decade. In every instance the correlation coefficients were higher in the former than in the latter (figure 3).

## PREDICTION OF THE NORMAL CAPACITY OF THE LUNGS

The highest correlation was found to be between the total capacity and the "radiological chest volume" at maximum inspiration. Therefore, knowing the "radiological chest volume" in a given case the corresponding total capacity may be predicted by means of the regression formula calculated from the correlation coefficient.[2] The subdivisions of the total capacity may be derived from the predicted value for this capacity by employing the average relative values found for these components.[3]

With the purpose of establishing the normal limits of variability, the values for the pulmonary capacity have been predicted for each individual of this series (figure 4). All of the observed values for the total capacity were within 20 per cent of the predicted ones, while for the vital capacity 98 per cent were within this percentage. The observed

[2] The regression formula is: Total capacity, liters = (0.31 × "radiological chest volume") + .71.

[3] The method of prediction is as follows: (a) The area of the pulmonary fields at maximum inspiration (measured on a roentgenogram) is 732 square centimeters. The external anteroposterior diameter of the chest at maximum inspiration is 23 centimetres. Hence, the "radiological chest volume" is $732 \times 23 = 16.8$ liters. (b) The corresponding total capacity would then be $(0.31 \times 16.8) + .71$ or 5.92 liters. (c) The vital capacity: $\frac{5.92 \times 75.5}{100} = 4.47$ liters. (d) The residual air is equal to the difference between the total and vital capacities or 1.45 liters. (e) The mid capacity: $\frac{5.92 \times 37.7}{100} = 2.23$ liters.

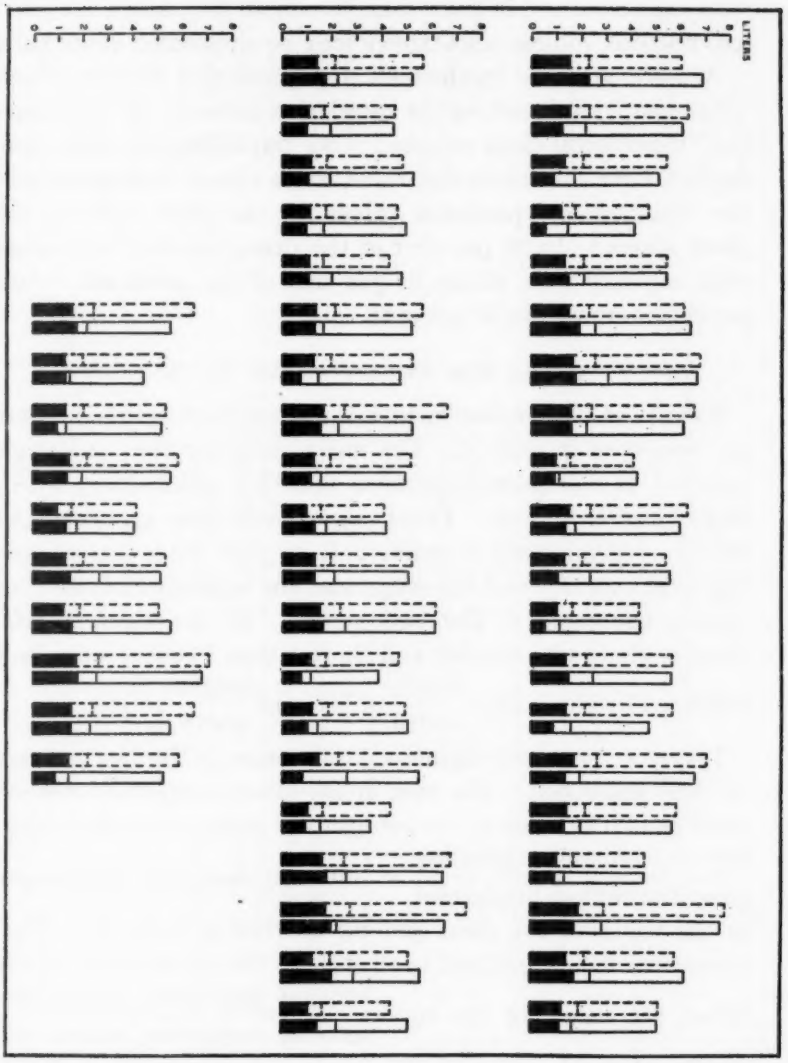



FIG. 4. Predicted and observed values for the pulmonary capacity in 50 healthy males between the ages of 38 and 63 years. Each individual is represented by two columns; the one on the left, with broken lines, is the predicted values; while the right-hand one is the observed values. The black area designates the residual air, the white space above is the vital capacity, while the whole column represents the total capacity. The line dividing the vital capacity is the mid capacity.

values for the total and vital capacities were within 15 per cent of the predicted one in 90 and 84 per cent of the cases respectively. A variation of more than 20 per cent from the predicted values in the total and vital capacities and of more than 40 and 50 per cent in the mid capacity and residual volume respectively may be considered abnormal.

A more accurate method for the prediction of the values for the vital capacity is based on the correlation between the vital capacity and the "radiological chest volume." By employing the regression formula derived from this coefficient there was a closer correspondence between the observed and predicted values for the vital capacity than those given above.[4] In 90 per cent of the cases the observed values for the vital capacity were within 15 per cent of the predicted values and 98 per cent were within 20 per cent.

### SHAPE, SIZE AND EXPANSION OF THE CHEST

Details of the various external and roentgenographic measurements are presented in table 8. The mean value for the "radiological chest volume" at maximum inspiration was 15.1 $\pm$0.23 liters with extremes of 11.2 and 20.9 liters. These values are in close agreement with those for the younger group of individuals, so that the several subdivisions of the total capacity and the shape and the expansion of the chest can be readily compared in the two groups. In the older individuals the chest tended to be circular and shorter than in the younger subjects, as indicated by the indices $\frac{\text{depth}}{\text{width}} \times 100$ and $\frac{\text{height}}{\text{width}} \times 100$.

Likewise there were significant differences in the two groups in regard to chest expansion. The men in the older group could not expand the chest as well as those in the younger age group, as indicated by the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$, excursion of the diaphragm, changes in the width of the chest and rib movement (table 8). The absolute differences were significant in all save for the excursion of the diaphragm. When the value for the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$ is greater than 71 and when the degree of movement of the rib is less than 9, a reduction in the expansion of the chest may be assumed to exist.

[4] The regression formula is: Vital capacity, liters = ("radiological chest volume" $\times$ 0.19) + 1.19.

TABLE 8

*Measurements on the shape, size and expansion of the chest*

| | MALES, 18–30 YEARS | | | MALES, 38–63 YEARS | | |
|---|---|---|---|---|---|---|
| | Mean | Standard deviation | Coefficient of variation | Mean | Standard deviation | Coefficient of variation |
| **External measurements** | | | | | | |
| | | | *per cent* | | | *per cent* |
| Lateral expansion, cm | 3.8 ±0.07 | 0.7 ±0.05 | 18.4 | 2.3 ±0.06 | 0.7 ±0.05 | 28.9 |
| Anteroposterior expansion, cm | 3.9 ±0.08 | 0.8 ±0.05 | 20.5 | 2.6 ±0.06 | 0.7 ±0.05 | 27.0 |
| **Roentgenographic measurements** | | | | | | |
| Excursion of diaphragm, cm.: | | | | | | |
| Right | 6.3 ±0.11 | 1.1 ±0.08 | 17.7 | 5.9 ±0.12 | 1.3 ±0.09 | 22.1 |
| Left | 6.4 ±0.12 | 1.2 ±0.09 | 18.7 | 6.2 ±0.13 | 1.3 ±0.09 | 21.8 |
| Expansion of chest width, cm | 3.2 ±0.08 | 0.8 ±0.06 | 25.0 | 2.9 ±0.07 | 0.8 ±0.05 | 26.3 |
| Rib movement, degree | 21.4 ±0.51 | 4.9 ±0.36 | 22.9 | 19.4 ±0.38 | 4.0 ±0.27 | 20.8 |
| $\frac{\text{Area at maximum expiration}}{\text{Area at maximum inspiration}} \times 100$ | 62.2 ±0.42 | 4.4 ±0.30 | 7.0 | 63.5 ±0.45 | 4.7 ±0.32 | 7.4 |
| Chest volume, expiration, liters | 7.5 ±0.10 | 1.10±0.07 | 14.6 | 8.5 ±0.14 | 1.5 ±0.10 | 17.2 |
| Chest volume, inspiration, liters | 14.8 ±0.17 | 1.82±0.12 | 12.2 | 15.1 ±0.23 | 2.4 ±0.16 | 15.6 |
| Area of pulmonary fields, expiration, $cm.^2$ | 425.0 ±5.77 | 55.5 ±4.08 | 13.0 | 416.0 ±6.14 | 64.4 ±4.34 | 15.5 |
| Area of pulmonary fields, inspiration, $cm.^2$ | 685.0 ±7.28 | 70.0 ±5.14 | 10.2 | 653.0 ±8.28 | 86.8 ±5.85 | 13.3 |
| Index $\frac{\text{height}^*}{\text{width}\dagger} \times 100$ | 67.6 ±0.77 | 8.1 ±0.55 | 11.9 | 70.5 ±1.02 | 10.7 ±0.70 | 15.2 |

* Average height of both diaphragms at expiration

† From roentgenogram at expiration

Contrary to previous results, in the present series the correlation between the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$ and the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ was low and insignificant, $+0.2315 \pm 0.0902$, and hence there appears to be no relation between chest expansion and the latter ratio.

### EFFECT OF AGE ON THE PULMONARY CAPACITY AND CHEST SIZE AND EXPANSION IN NORMAL MALE SUBJECTS

When the values for the pulmonary capacity were grouped according to decades it was noted that there was a gradual decrease in the values for the total and vital capacities from the average age of 23 years to 64 years, except for the sixth decade where the values were slightly higher than for the preceding decade (table 9). This may be readily explained on the basis of chest size, expressed as the "radiological chest volume" at maximum inspiration. This volume was practically the same, 14.8 liters, for the third, fifth and seventh decades, while for those individuals in the sixth decade it was 1.1 liter greater. Likewise there was a gradual diminution in the components of the vital capacity, the complementary and reserve volumes. Age had no significant influence on the mid capacity, but there was a gradual increase in the residual volume from 1.19 liters with an average age of 23 to 1.58 liters at 64 years. These absolute differences were reflected in the relative values. With increasing years, the residual air constituted a larger percentage of the total capacity, from 19.8 per cent in the third decade to 31.5 in the seventh.

Age likewise had its influence upon the shape of the chest. The anteroposterior diameter of the chest tends to approach the lateral diameter as the age increases. The ability of the individual to expand the chest gradually decreases from the third to seventh decade, as indicated by a progressive diminution in the excursion of the diaphragm and rib movement and by an increase in the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$.

In figure 5 and table 10 the values for the total and vital capacities and the residual air have been predicted by the formula derived from a study of 50 normal male subjects between the ages of 18 and 30 years (2). The observed values are expressed as percentages of the predicted ones. The effect of age on the total and vital capacities is amply depicted

TABLE 9

*Comparison of the mean values for pulmonary capacity and chest size and expansion in normal males of various age groups*

| PULMONARY CAPACITY | 18–30 YEARS (AVERAGE 23 YEARS) MEAN | 38–50 YEARS (AVERAGE 44 YEARS) MEAN | 50–60 YEARS (AVERAGE 53 YEARS) MEAN | 60–76 YEARS (AVERAGE 64 YEARS) MEAN |
|---|---|---|---|---|
| Number of cases | 50 | 34 | 10 | 8 |
| **Absolute values** | | | | |
| | *liters* | *liters* | *liters* | *liters* |
| Total capacity | 5.97 ±0.08* | 5.40 ±0.10* | 5.62 ±0.13* | 5.01 ±0.22* |
| Vital capacity | 4.78 ±0.06 | 4.12 ±0.07 | 4.18 ±0.09 | 3.43 ±0.16 |
| Mid capacity | 2.18 ±0.05 | 1.98 ±0.06 | 2.28 ±0.12 | 2.04 ±0.10 |
| Complementary air | 3.79 ±0.05 | 3.42 ±0.06 | 3.34 ±0.12 | 2.97 ±0.18 |
| Reserve air | 0.98 ±0.02 | 0.70 ±0.03 | 0.84 ±0.08 | 0.46 ±0.05 |
| Residual air | 1.19 ±0.03 | 1.28 ±0.05 | 1.44 ±0.09 | 1.58 ±0.09 |
| **Relative values (total capacity = 100 per cent)** | | | | |
| Vital capacity | 80.2 ±0.45 | 76.6 ±0.58 | 74.5 ±1.26 | 68.5 ±1.07 |
| Mid capacity | 36.2 ±0.52 | 36.0 ±0.64 | 40.6 ±1.98 | 41.1 ±1.73 |
| Complementary air | 63.9 ±0.52 | 64.0 ±0.65 | 59.4 ±1.91 | 58.9 ±1.53 |
| Reserve air | 16.8 ±0.56 | 12.6 ±0.54 | 15.1 ±1.53 | 9.6 ±1.17 |
| Residual air | 19.8 ±0.42 | 23.4 ±0.56 | 25.5 ±1.44 | 31.5 ±1.25 |
| **Relative values (vital capacity = 100 per cent)** | | | | |
| Mid capacity | 45.8 ±0.81 | 47.3 ±1.15 | 55.6 ±3.42 | 60.9 ±3.80 |
| Complementary air | 79.4 ±0.50 | 83.2 ±0.68 | 79.7 ±1.90 | 85.9 ±1.57 |
| Reserve air | 20.6 ±0.52 | 16.7 ±0.66 | 20.3 ±1.93 | 14.1 ±1.72 |
| Residual air | 25.1 ±0.66 | 30.0 ±0.97 | 35.3 ±2.59 | 46.8 ±2.88 |
| **Expansion and size of the chest** | | | | |
| Excursion of the diaphragm, cm.: | | | | |
| Right | 6.3 ±0.11 | 5.9 ±0.15 | 6.0 ±0.30 | 5.7 ±0.31 |
| Left | 6.4 ±0.12 | 6.0 ±0.15 | 6.0 ±0.27 | 5.2 ±0.43 |
| Lateral expansion, cm | 3.2 ±0.08 | 3.1 ±0.09 | 2.7 ±0.13 | 2.2 ±0.32 |
| Rib movement, degrees | 21.4 ±0.51 | 19.9 ±0.45 | 18.8 ±0.83 | 15.9 ±0.97 |
| $\frac{\text{Area at maximum expiration}}{\text{Area at maximum inspiration}} \times 100$ | 62.2 ±0.42 | 64.1 ±0.46 | 64.5 ±1.33 | 64.9 ±1.17 |
| Radiological chest volume, maximum inspiration, liters | 14.8 ±0.17 | 14.8 ±0.26 | 15.9 ±0.38 | 14.7 ±0.79 |
| Index $\frac{\text{depth}}{\text{width}} \times 100$ | 68.5 ±0.55 | 73.9 ±0.62 | 75.2 ±0.35 | 75.9 ±0.95 |
| Index $\frac{\text{height}\dagger}{\text{width}\ddagger} \times 100$ | 67.6 ±0.77 | 70.9 ±1.13 | 73.4 ±2.4 | 70.4 ±3.03 |

* Probable error

† Average height of both diaphragms at expiration

‡ From roentgenogram at expiration

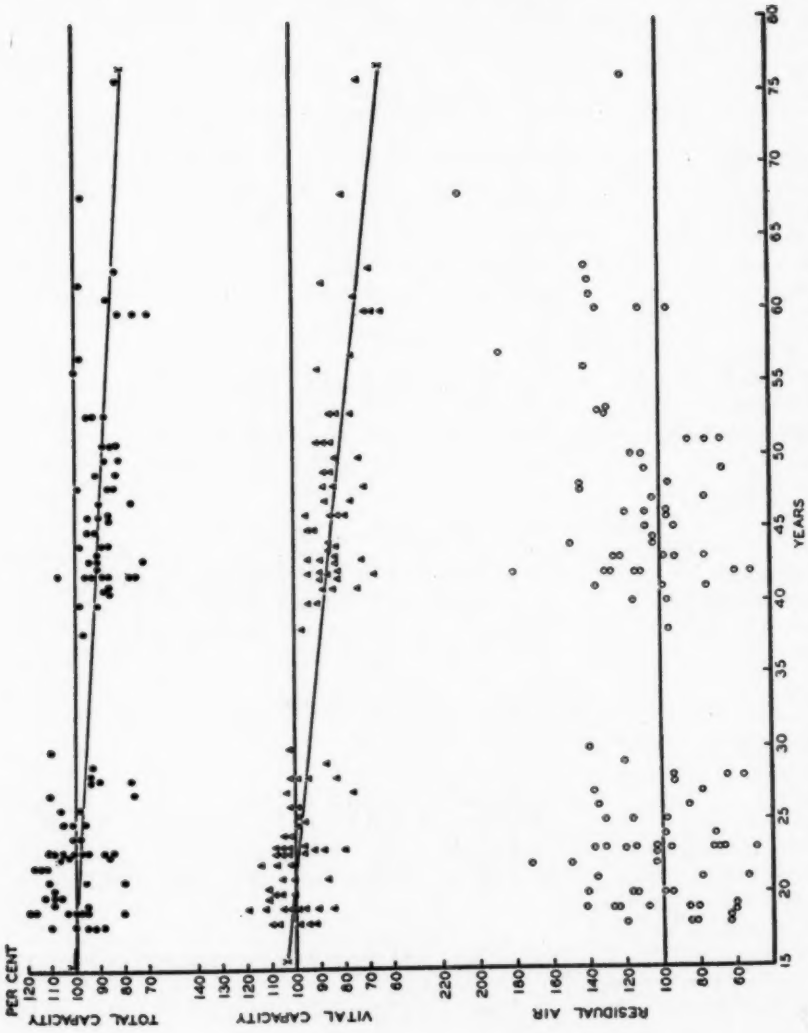



FIG. 5. The influence of age on the total and vital capacities and the residual air

by the straight line. The influence of age on the residual air was less marked, but after 55 years of age the values for this capacity were increased in every case. When the absolute values were predicted on the basis of the chest size for each individual, there was a gradual decrease in the total and vital capacities from the third to the eighth decade.

TABLE 10

*Effect of age on the pulmonary capacity*

| AGE | NUMBER OF CASES | PER CENT OF PREDICTED* | | | RESIDUAL AIR / TOTAL CAPACITY × 100 |
|---|---|---|---|---|---|
| | | Total Capacity | Vital Capacity | Residual Air | |
| *years* | | | | | *per cent* |
| 15–25 | 37 | 101 | 101 | 100 | 19.3 |
| 25–35 | 13 | 96 | 95 | 103 | 20.8 |
| 35–45 | 21 | 90 | 85 | 107 | 23.5 |
| 45–55 | 21 | 87 | 84 | 104 | 23.3 |
| 55–65 | 8 | 87 | 75 | 136 | 30.8 |

* Prediction from the following regression equation: Vital capacity (liters) = (Radiological chest volume × 0.24) + 1.22

## DISCUSSION

From the above results it appears that the effect of age on the absolute values of the pulmonary capacity is in the direction of those alterations usually found in cases with chronic abnormalities of the cardiorespiratory systems, that is, a decrease in the total and vital capacities and an increase in the residual air and mid capacity. Detecting abnormalities in patients with such disorders resolves itself into the question of degree and it is, therefore, necessary to correct these volumes for the proper age group. These results, along with those previously reported (2), indicate that the most useful capacities for classifying respiratory dysfunction are the total and vital capacities and the relationship between the residual air and the total capacity. When the values for the former deviate more than 20 per cent and when the residual air constitutes more than 40 per cent of the total capacity structural abnormalities may be suspected.

Repeated measurements of the pulmonary capacity in the same individuals have shown great constancy. This is very valuable in following the course of a given case, such as has recently been made in cases of lobar pneumonia (22) or during the transition from congestive heart failure to a state of compensation.

It is of interest to consider the factors which are responsible for the

gradual reduction in the total and vital capacities and the slight rise in the residual air from youth to old age. The degenerative changes in the thorax and spine are probably the most important factors that will limit maximum inspiration and thus cause a reduction in the total capacity and limit maximum expiration, thereby reducing the vital capacity. Since the maximum expiratory level is not reached, all the reserve air is not expelled, thus increasing the residual volume of the lungs. Another factor in addition to the reduced mobility of the chest is the loss of elasticity of the parenchyma of the lungs and the bronchial tree. With impairment of this tissue the above alterations wili be augmented. Christie (23) recently has proposed a simple test for the detection of alterations in the pulmonary elasticity and terms it the "over-distension test." Normally, when the reserve and complementary volumes are recorded separately, the expiratory level immediately after maximum deflation and inflation returns to the previous level. Also, the sum of the reserve and complementary volumes approximates the value for the vital capacity when this volume is taken in the usual clinical fashion, that is, complete expiration following maximum inspiration. Christie demonstrated in cases of obstructive emphysema where there is a loss of pulmonary elasticity that the expiratory level did not return immediately to the previous level following maximum deflation or inflation, but that it gradually rose or fell by a series of steps to the original level. Likewise he noticed partial or complete disappearance of the reserve air after a maximum inflation. These tests were performed on the 50 normal subjects in this series and the results show that there was a decrease of more than 200 cc. in the reserve air in 20 cases (40 per cent) following maximum inflation as compared with the volume when it was recorded separately. In the same number of individuals the expiratory level did not reach the original one immediately but gradually returned by a series of steps. These abnormalities of the spirometric tracings in this group of older men may well be due not only to a slight impairment of pulmonary elasticity but also to decreased mobility of the chest cage. Additional evidence of impairment of pulmonary elasticity, accompanied by an increase in the size of the lungs at maximum expiration, has been recently demonstrated by Prinzmetal and Kountz (24) who found that during the fourth decade there was a gradual reduction both in vital capacity and in the ability of the individual to lower the intrapleural pressure. They ascribed these alterations to a decrease in the power of the respiratory muscles and a loss of elasticity of the lungs.

Another factor responsible for the decrease in vital capacity which has been suggested is weakened general musculature and lack of exercise. This does not seem to be so in this series of men. The individuals in this group were mainly men who have been accustomed to and are still engaged in moderately severe work, so that their muscular system should be as efficient or more so than that of those in the third decade who were students.

When the individuals in the present series are grouped according to their occupations, it appears that the values for the vital capacity are independent of the degree of physical activity. The residual air and mid capacity were somewhat higher in the group of men engaged as mechanics and laborers than those in professions, although the volume of the chest was smaller in the former than in the latter group. However, in a larger series of cases this may not be true.

## SUMMARY AND CONCLUSIONS

Determinations of the total pulmonary capacity and its subdivisions and roentgenographic measurements were made on a series of 50 normal males between the ages of 38 and 63 years. It has been shown that the pulmonary capacity may be predicted from the "radiological chest volume" at maximum inspiration with a reasonable degree of accuracy. The method of calculation has been presented in detail. The results of this series have been compared to those of a group of male subjects in the third decade previously reported (1, 2). The effect of age on the pulmonary capacity and shape and expansion of the chest has been presented. The influence of posture (lying and sitting) on the pulmonary capacity and size and expansion of the chest has been demonstrated.

The observations presented suggest the following conclusions:

1. In normal male subjects of the fifth and sixth decades there are marked variations in the absolute values of the pulmonary capacity. There are high correlations between the vital and total capacities and the "radiological chest volume" at maximum inspiration. From the correlation coefficient a formula has been developed which permits the prediction of the normal pulmonary capacity in any given case.

2. A variation from the predicted values of more than 20 per cent in the observed total and vital capacities, and of more than 40 and 50 per cent in the mid capacity and residual air respectively, may be considered beyond the normal limits of variations.

3. The vital capacity, residual air and mid capacity expressed as percentages of the total capacity vary within well defined limits. When

the residual air constitutes more than 40 per cent of the total capacity, it may be considered significant.

4. When a subject changes from a sitting to a recumbent position the total and vital capacities and the residual air decrease slightly, the reserve air moderately, while there is a moderate increase in the complementary air.

5. There is a definite correlation between the respiratory dead space and the tidal volume, independent of the respiratory rate.

6. The expansion of the chest can best be determined by roentgenographic measurements. If the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$ exceeds 71 per cent and if the rib movement from maximum expiration to inspiration is less than 9 degrees, chest expansion may be considered to be abnormally small.

7. Age causes a gradual progressive decrease in the total and vital capacities from the third decade to the eighth. The residual air does not appear to be affected until after the fifty-fifth year. From youth to old age the ability to expand the chest gradually diminishes, as indicated by the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$, excursion of the diaphragm, lateral expansion of the chest and rib rotation.

8. The factors responsible for the effect of age on the pulmonary capacity and chest expansion have been discussed.

## REFERENCES

(1) HURTADO, A., AND BOLLER, C.: Studies of total pulmonary capacity and its subdivisions. I. Normal, absolute and relative values, Jour. Clin. Invest., 1933, *12*, 793.

(2) HURTADO, A., AND FRAY, W. W.: Studies of total pulmonary capacity and its subdivisions. II. Correlation with physical and radiological measurements, Ibid., 1933, *12*, 807.

(3) CHRISTIE, R. V.: The lung volume and its subdivisions. I. Methods of measurement, Ibid., 1932, *11*, 1099.

(4) HURTADO, A., FRAY, W. W., KALTREIDER, N. L., AND BROOKS, W. D. W.: Studies of total pulmonary capacity and its subdivisions. V. Normal values in female subjects, Ibid., 1934, *13*, 169.

(5) LASSEN, H. C. A., COURNAND, A., AND RICHARDS, D. W., JR.: Distribution of respiratory gases in a closed breathing circuit. I. In normal subjects, Ibid., 1937, *16*, 1.
COURNAND, A., LASSEN, H. C. A., AND RICHARDS, D. W., JR.: Distribution of respiratory gases in a closed breathing circuit. II. Pulmonary fibrosis and emphysema, Ibid., 1937, *16*, 9.

(6) BOWEN, B. D., AND PLATT, D. L.: The relation of age and obesity to vital capacity, Arch. Int. Med., 1923, *31*, 579.

(7) LEMON, W. S., AND MOERSCH, H. J.: Factors influencing vital capacity, Ibid., 1924, *33*, 136.

(8) HUTCHINSON, J.: On the capacity of the lungs and on the respiratory functions, Medico-Chirurgical Trans., 1846, *29*, 137.

(9) PRATT, J. H.: Long-continued observations on the vital capacity in health and heart disease, Amer. Jour. Med. Sci., 1922, *164*, 819.

(10) MYERS, J. A., AND MAEDER, L. M. A.: Studies on the respiratory organs in health and disease. XIV. The vital capacity of the lungs of 419 firemen, Arch. Int. Med., 1925, *35*, 184.

(11) MCKEAN, R. M.: Lowered vital capacity of the lungs in a case of primary hepatic tumor with pulmonary metastases, Amer. Jour. Med. Sci., 1922, *163*, 710.

(12) CORNET, G.: Inaugural dissertation, München, 1884. Quoted from MYERS, J. A., AND CADY, L. H.: Amer. Rev. Tuberc., 1924, *9*, 57.

(13) WINTRICH, M. A.: Handbuch. d. spec. Path. und Therap. (Virchow), 1854. Quoted from MYERS, J. A., AND CADY, L. H.: Amer. Rev. Tuberc., 1924, *9*, 57.

(14) PIOLTI, M.: Recherches sur la capacité vitale pulmonaire, Biol. méd., 1930, *20*, 198.

(15) MYERS, J. A., AND CADY, L. H.: Studies of the respiratory organs in health and disease. XIII. The effects of senility on the vital capacity of the lungs, Amer. Rev. Tuberc., 1924, *9*, 57.

(16) LEVISON, L. A.: Vital capacity with respect to diagnosis and prognosis, Ohio State Med. Jour., 1923, *19*, 89.

(17) LEVY, B.: Die Vitalkapazität im höheren Lebensalter, Zentralbl. f. inn. Med., 1933, *54*, 417.

(18) HURTADO, A., AND FRAY, W. W.: Studies of total pulmonary capacity and its subdivisions. III. Changes with body posture, Jour. Clin. Invest., 1933, *12*, 825.

(19) HALDANE, J. S., AND FITZGERALD, M. P.: The normal alveolar carbonic acid pressure in man, Jour. Physiol., 1905, *32*, 486.

(20) HALDANE, J. S., AND PRIESTLEY, J. G.: The regulation of the lung-ventilation, Ibid., 1905, *32*, 225.

(21) HALDANE, J. S.: The variations in the effective dead space in breathing, Amer. Jour. Physiol., 1915, *38*, 20.

(22) KALTREIDER, N. L., HYDE, H. v. Z., AND FRAY, W. W.: Pulmonary capacity in lobar pneumonia with special reference to collapse therapy, Arch. Int. Med., 1937, *59*, 408.

(23) CHRISTIE, R. V.: The elastic properties of the emphysematous lung and their clinical significance, Jour. Clin. Invest., 1934, *13*, 295.

(24) PRINZMETAL, M., AND KOUNTZ, W. B.: Intrapleural pressure in health and disease and its influence on body function, Medicine, 1935, *14*, 457.

# NONCASEATING TUBERCULOSIS[1]

## An Analysis of the Literature

MAX PINNER

In a brief preliminary report (157 a) I have tried to outline the various clinical and pathological pictures that constitute the domain of noncaseating tuberculosis. The opinion was expressed that Boeck's sarcoid, *ostitis tuberculosea multiplex cystoides*, uveoparotid fever, certain cases of Mikulicz's syndrome and a number of disseminated pulmonary and lymph node lesions are the main representatives of noncaseating tuberculosis. The purpose of this report is to present an analysis of the available facts and observations in the literature that may support the contention made in the former communication.

It is, therefore, not my aim to give a full clinical pathological description of the diseases mentioned; this knowledge is rather presupposed and adequate references are provided. I wish to present those data that seem pertinent in answering the two main questions:

(*1*) Are the diseases enumerated identical in essence and simply different manifestations of the same morbid process?
(*2*) Is their aetiology the tubercle bacillus and their pathogenesis a particular phase of the disease tuberculosis?

The bibliography that is appended is not complete. A considerable number of papers that have been read in the preparation of this report are omitted because they do not contain any data related to the two main questions mentioned. Only those papers are included that are specifically referred to in the text. Undoubtedly, pertinent reports have been overlooked, since these papers are scattered through journals devoted to almost any conceivable specialty, and a number of known papers were, on account of linguistic barriers, available only in brief abstracts.

However, it is hoped that the material presented is sufficient to make an affirmative answer to the two main questions appear to be a reasonable

[1] From the Laboratory of the Hermann M. Biggs Memorial Hospital, Ithaca, New York.

working hypothesis, and to show where further work is necessary to transform eventually this hypothesis into a convincing assumption and finally into proved fact.

## BOECK'S SARCOID

The terminology of Boeck's sarcoid is confusingly and unnecessarily involved, partly due to the fact that artificial subdivisions have been suggested, particularly in regard to the dermatological morphology, partly because the recognition that other than cutaneous lesions form an essential part of the disease has been a slow gradual development, and partly because a number of authors attempted to include in the diagnostic terms their own opinion as to aetiology, prognosis and general appearance.

The more common diagnostic terms used for the manifestations are: multiple benign sarcoid; multiple benign lupoid; sarcoidosis; Boeck's, Besnier's, Hutchinson's, Mortimer's or Schaumann's disease (or any combination of the foregoing names); miliary lupoid; *tuberculosis indurativa lupoides* (type Boeck); benign lymphogranulomatosis.

The early history of the disease, as first described by Boeck (16),[2] is well discussed by Hunter. In its cutaneous manifestations it is essentially identical with the subcutaneous sarcoids (Darier and Roussy (33)), with lupus pernio (Besnier), with angiolupoid (Brocq and Pautrier), and probably, but more questionably so with erythema induratum Bazin. The opinion that these various dermatological conditions are essentially identical is extensively discussed by Volk (207), and more recently by Grschebin and Proppe. The main differences between these dermatological manifestations are those of localization which do not obscure their morphological and histogenetic unity.

### *Distribution of Lesions*

The main development in the knowledge of Boeck's sarcoid is in the realization that it is potentially a generalized disease in which skin manifestations are frequent but not constant. On the basis of clinical observation, supported by bioptic findings, there is hardly any organ system that has not been found involved. While in many cases it is easy to suspect the diagnosis of Boeck's sarcoid, a positive diagnosis is impossible without bioptic study. I shall, therefore, accept the involvement of a

[2] Reference numbers are given only when the author's name is not mentioned, or when the Bibliography contains more than one paper by the respective author.

TABLE 1

*Summary of autopsies of 18 cases of Boeck's sarcoid*

| REPORTED BY | CAUSE OF DEATH | SKIN | LUNG | LYMPH NODES | BONE MARROW | SPLEEN | LIVER | TRACHEA-BRONCHI | TONSILS | KIDNEY | INTESTINAL TRACT | OTHER ORGANS | ASSOCIATED LESIONS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schlagenhaufer (quoted by Kyrle, 1914, (105) | Not stated, incomplete report | | + | + | | + | | | | | | | |
| Strümpke, 1920, (197) | Pulmonary tuberculosis | + | | | | | | | | | | | |
| Schaumann, 1922, (186) | Influenza | | + | + | + | + | + | | | | | | |
| Schaumann, 1922, (186) | Pulmonary tuberculosis | + | | | + | + | | | | | | | Caseous tuberculosis of tracheobronchial and mesenteric lymph nodes; ulcerative tuberculosis of ileum |
| Michalik, 1924, (129) | Sepsis | + | | | | | | | | | | Palate | Pulmonary tuberculosis |
| Bernstein, *et al.*, 1929, (11) | Bilateral hydrothorax | + | | + | | | | + | | | + | Epicardium | |
| Lenartowitz, *et al.*, 1930, (111) | Sarcoid in region of optic chiasm | + | + | | + | + | | + | | | + | Brain | Ulcerative tuberculosis of ileum and colon; pulmonary tuberculosis |
| Schaumann, 1933, (187) | Emphysema | + | + | + | + | + | + | | + | + | | | |
| Beintema, 1934, (7) | Angiomatosis retinae; cystoma cerebri (incomplete) | | + | | | | | | | | | | |
| Tillgren, 1935, (202); Schaumann, 1936, (190) | Sarcoid lesion in pituitary | | + | + | + | + | + | + | + | | + | Pituitary, epididymis, prostate, renal capsule | Diabetes insipidus; miliary tubercles in peritoneum |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Danbolt, *et al.*, 1936, (32) | Carcinoma | + | + | + | + | + | | | | | | Emphysema |
| Nickerson, 1937, (141) Case 1 | Massive sarcoidosis | | + | + | + | + | + | | | | Eyelid, heart | |
| Nickerson, Case 2 | Cardiac decomposition, bronchopneumonia | | | | + | + | + | | | | Testis | |
| Nickerson, Case 3 | Lobar pneumonia | | | | + | + | | | | | | |
| Nickerson, Case 4 | Cerebellar haemorrhage | | + | + | + | + | + | | | | Pancreas | |
| Nickerson, Case 5 | Ruptured aneurism of cerebral artery | | + | | | | + | | | | | |
| Nickerson, Case 6 | Lobar pneumonia | | + | + | + | + | + | | | | | |
| Pinner, 1937, (157) | Pulmonary tuberculosis | + | + | + | + | + | | | | + | | |

given organ only if confirmed by histological findings. For this reason it is probably best to present the evidence of the distribution of lesions first on the basis of the reported autopsies (table 1).

However, the relatively few autopsy reports do not yield the correct frequency of distribution, first, on account of their small numbers, second, because, as Schaumann emphasizes particularly, some sarcoid lesions disappear when a progressive tuberculosis supervenes, and, third, because in some of the reports it is not stated which organs were and were not examined.

Some of the more rarely observed localizations, according to clinical and bioptic studies, are: mucosa of nose (6, 18, 79, 92, 94, 117, 124, 130, 164, 203), pharynx (13, 117), larynx (13, 115), conjunctiva (17, 92, 93, 137, 196), striated muscle (9, 117, 198), mammary gland (196), knee joint (22), epididymis (77), colon (114), eyelid (44), and peripheral nerve (126). (This latter observation has been questioned, since it seems more than likely that leprosy was the correct diagnosis.) To these must be added involvement of iris, lachrymal and salivary glands; these will be discussed in greater detail in the paragraph *Associated Lesions*, where the pertinent references will be found.

The relative frequency of the major lesions, particularly of those demonstrable by roentgenological methods, should be judged only by the observations of rather recent years since the recognition of sarcoid as a generalized disease became established.

*Lymph nodes* are involved in the majority of all patients. Schaumann (190) states that he has found lymphatic involvement in all his clinical cases and that in his 21 active cases in which the tonsils were examined they were found involved. The lymph node involvement is frequently independent of lesions peripheral to their respective region of drainage. Both peripheral and visceral lymph nodes are affected. Martenstein (123) states that of 34 cases with chest roentgenograms 31 per cent showed enlargement of hilar lymph nodes. The apparent rarity of involvement of intraäbdominal nodes is probably simulated by the difficulty of their detection.

*Bones:* The actual frequency of bone lesions is impossible to judge, partly because many cases were never examined roentgenologically and partly because a considerable number of cases with bone lesions have been described as a separate disease without due regard to associated foci elsewhere in the body. Nielsen, who has made a special study of the osseous lesions in sarcoid, reports that approximately 20 per cent of

patients with Boeck's sarcoid, examined at the Finsen Institute, had demonstrable bone lesions. It seems likely from the literature that the dermatological manifestations of lupus pernio are more frequently associated with skeletal lesions. A further discussion of bone lesions will be presented in the section on *ostitis tuberculosea multiplex cystoides*.

*Lungs:* The pulmonary lesions, apparently first described by Kuznitzky and Bittorf (103) consist of more or less evenly and symmetrically distributed small foci whose seeding is usually denser in the middle and lower portions of the lungs than in the apices. At times the lesions suggest a diffuse fibrosis with stringy, rather dense shadows in web-like arrangement, radiating from the hilum toward the periphery. They are distinguished by the absence of exudative features and by their stability. The character of the roentgenological shadows is by no means uniform; Their variations are probably best indicated by the fact that the following differential diagnostic considerations are often in order from a strictly roentgenological point of view: miliary tuberculosis, miliary carcinomatosis, diffuse nonspecific or posttuberculous fibrosis, pulmonary congestion. A definite roentgenological diagnosis is probably impossible; it must depend on the histological nature of associated lesions, although the simultaneous occurrence of cystic bone foci or the rather characteristic clinical course may make the diagnosis highly suggestive.

It seems quite likely that the multiplicity of roentgenological appearances is, at least in part, an expression of the different age of the pulmonary lesions. The more fibrotic and stringy lesions are probably the older ones, since—as will be discussed later—*one* potential development of the sarcoid tubercle is fibrosis. Nielsen mentions the possibility of resorption. Freund observed considerable clearing during four years' observation, Valentini during three years' observation. Longcope and Pierson describe complete disappearance of hilar and parenchymal lesions in the course of six years (case 2) and in the course of ten years (case 3). However, the roentgenological life history of pulmonary sarcoid still needs considerable clarification.

The roentgenological character of intrathoracic sarcoid has been described in many individual case reports. Careful studies on series of cases have been presented by Nielsen. Of his 46 patients with cutaneous sarcoid, 39 had a roentgenological examination of the chest, and 37 of them showed pulmonary lesions. Representative case reports are published for example by Pautrier (151, 152), Kuznitzky (102), and Held (71). However, a number of cases have been reported without

cutaneous, but with pulmonary lesions (for example: Freund, Nonnenbruch, Bödeker, Waldenström (210), cases 1, 3, 5 and 8 of Longcope and Pierson). More from postmortem than from roentgenological evidence, it is known that fibrosis and concomitant emphysema may develop (Schaumann (187), Hudelo and Rabut (76)). Consistent with this is the occasional finding of polycythaemia (13, 183) in patients with long standing pulmonary sarcoid.

A distinct help in the diagnosis of pulmonary sarcoid is the spectacular discrepancy between the massive anatomical involvement and the paucity or absence of respiratory symptoms and physical signs. In this regard it seems that all observers are in complete agreement.

A great deal of uncertainty, however, exists in regard to diagnosis, and as corollary, in regard to the question which cases should be included in the group of pulmonary sarcoid. Strictly speaking, the diagnosis can only be made at autopsy and by histological examination of the lesions. When, however, associated lesions are available for biopsy, it is probably safe to assume that pulmonary foci of characteristic roentgenological appearance are of the same nature as the lesions determined by biopsy, usually in lymph nodes or skin, more rarely in tonsils or mucous membranes. It would seem justifiable to make the diagnosis in some cases without bioptic evidence, when symptomatology, physical findings and roentgenological appearance are characteristic. This might be done with increased confidence if, as mentioned before, cystic bone lesions are demonstrable, if iritis is coëxisting or has occurred previously, if tuberculin allergy is low or not demonstrable and if there exists a monocytosis.

There can be no doubt that many cases of pulmonary sarcoid have been reported under a great variety of names. It seems impossible at the present time to assign every case to its proper classification in the absence of any absolute pathognomonic signs and symptoms, save histological examinations. The various names under which pulmonary sarcoid has been reported include frequently both sarcoid and other conditions, chiefly banal tuberculosis. It is not assumed that all cases under the designations to be enumerated presently are sarcoid; but it seems highly probable that *some* cases in each group are actually sarcoid. The names under which we are likely to find some cases of pulmonary sarcoid are: chronic miliary tuberculosis (Assman and Held (70)); tuberculids of the lung (Bödeker); sclerosing, tuberculous, large-cell hyperplasia (Mylius and Schürmann (138)); certain so called atypical cases of tuber-

culosis (Gebsattel, Esser); *granulie discrète* of Bard; *tuberculosis miliaris discreta* of Neumann; benign pulmonary tuberculosis (Nonnenbruch); torpid forms of disseminated tuberculosis (Hantschmann); *lymphangitis reticularis* (Hansemann, Schürmann); *granulie froide* and *tramite* of the French authors; haematogenous, nonmiliary pulmonary tuberculosis (Pinner (156)). This list does not claim completeness.

Many cases reported under the above classification are not described in sufficient detail to warrant definite conclusions, others show some of the features that were mentioned above as circumstantial evidence in favor of sarcoid, and a few had associated lesions that were bioptically diagnosed as sarcoid.

These lesions are of particular importance because they occur in the majority of patients with Boeck's sarcoid, because they are not infrequently the only demonstrable lesions and because they are frequent in some of the other clinical entities that belong probably in the great and polymorphous group of noncaseating tuberculosis. It seems likely that it is essentially on the basis of these lesions that it will be possible at some future time to determine with greater accuracy than is possible to-day which clinical pictures belong to the field of noncaseating tuberculosis. Before ending this paragraph on localization and distribution of lesions it must be emphasized again that pulmonary sarcoid occurs without cutaneous manifestations (188, 213, 214).

### *Histology*

The histological appearance of sarcoid lesions has been described and discussed in some detail by Boeck (16, 17, 18), Ehrmann, Maloney and Combes, describing the Darier-Roussy type, Pautrier (153), Schaumann (182), Kyrle (104, 107), Kissmeyer (92, 94), Longcope and Pierson and many others.

It has been stated repeatedly that the absolute diagnosis of sarcoid is possible only by histological examination. Histologically, the lesions consist of tuberculoid accumulations of epithelioid cells, frequently, but not always, surrounded by a thin layer of lymphocytes. Within the epithelioid follicles, occasional giant cells of the Langhans type are seen. Necrosis and caseation are absent, although single epithelioid cells may show some slight necrobiotic changes; exudative features and polymorphonuclear cells are absent. This is the diagnostic picture of sarcoid that is seen and reported with monotonous uniformity; and it is probably the only histological picture by which the diagnosis can be established.

However, it is self-evident that the picture, as described, cannot encompass the entire life cycle of the lesion. It apparently does not include the earliest phases nor the late phases that, according to clinical and roentgenological observations, must include resorption and fibrosis.

As far as the early phase is concerned, Kyrle (107) has observed a case with three fairly acute exacerbations of cutaneous sarcoid, and he has taken biopsies at brief intervals. The skin eruption, preceded by fever, was first characterized by a simple erythema. Within the first ten days there was a simple inflammatory exudate in which lymphocytes predominated. Typical sarcoid structures were found from the eleventh day on; about the thirty-sixth day a fair number of giant cells were present; on the fifty-eighth day the epithelioid cells showed vacuolization and degeneration and there was some young granulation tissue. Healing occurred with an atrophic scar.

The available knowledge concerning the late regressive changes has accumulated during recent years. Schaumann (183) found in biopsy specimens of bone marrow and lymph nodes what he termed *une transformation sclèreuse.* In autopsy material (190), he and others (12, 138, 157) observed the same fibrous sclerosis, consisting either of encapsulating fibres around epithelioid granulomata or of a complete replacement of the granulomata by fibrosis. The fibrosis is characterized by particularly heavy, coarse hyaline fibres that frequently stain orange or yellowish with van Gieson, indicating probably some degenerative process. The hyalinized granuloma, according to my own observations, has not the appearance that fibrosed tubercles usually have; the fibrosis is coarser and shows practically always the atypical tinctorial reaction that Schaumann has pointed out. It would seem that this hyalinization must occur rapidly: in two cases in which I found these changes associated with typical sarcoid structures, I have not been able to find intermediate stages. That is, granulomata that are partly hyalinized are frequent, but a histogenetic phase between epithelioid cells and hyaline fibrosis, such as young fibroplastic tissue, I have not been able to find.

### *Autopsies*

In the literature I have found 17 autopsy reports on patients with sarcoid lesions; to this I can add one case (see table 1). Out of these 18 cases, shown in table 1, 10 died of causes either not related to sarcoid or of causes not fully stated. In the remaining 8 cases, sarcoid or its consequences was the direct cause of death. In 2 cases (111, 202) the par-

ticular localization of the lesions is responsible for the fatal issue. In only one case (Nickerson (141), case 1) is it assumed that the massiveness of the general involvement *per se* caused death. One case died with emphysema as the outstanding lesion, while it occurred in others too. It is evident from these reports that the massive and diffuse hyalinization of the intrapulmonary granulomata was the direct cause of the fibrosis and concomitant emphysema. These observations of sarcoidal pulmonary sclerosis and emphysema lend a solid anatomical basis to the roentgenological interpretation, mentioned above, of fibrosis developing following sarcoid lesions in the lung.

In four of the 18 autopsy cases, pulmonary tuberculosis was the cause of death; but in a few other cases less significant tuberculous foci were found in addition to the major lesions. These cases present squarely the question as to the relation, if any, between sarcoid and frank tuberculosis. I can fully confirm Schaumann's impression that frank, caseating tuberculosis in these cases seems to be a direct transformation of the sarcoid lesions and not an added, separate process. This impression is gained by the fact that small caseous centres are found in foci that otherwise present typical sarcoid structure. Single foci may accordingly present typical tuberculous and sarcoid features. In both of Schaumann's cases the cutaneous manifestations of sarcoid (lupus pernio) disappeared simultaneously with the development of bacilliferous tuberculosis. In two other cases, Schaumann (189) made the identical clinical observation of disappearing cutaneous sarcoids at the time of the appearance of tuberculosis and the development of hitherto absent tuberculin allergy (similar observations (60)). The interrelation between sarcoidal structure, tuberculin allergy and caseating tuberculosis will be discussed in greater detail later on.

In practically all autopsies more lesions were found than were clinically diagnosed. This applies particularly to lymph nodes, intraäbdominal and intrathoracic, and to bone marrow in locations that had not shown roentgenologically demonstrable foci. It is striking that the most frequent site of sarcoid involvement follows closely the pattern of distribution in miliary tuberculosis; lymph nodes, lung, liver, spleen and bone marrow being the most frequently affected tissues.

### *Bacteriology*

Considering the great number of attempts to demonstrate tubercle bacilli in the specific lesions, the relatively few positive results are not

TABLE 2

*Positive bacteriological findings in Boeck's sarcoid*

| AUTHOR | LESION | SECTION | CULTURE | ANIMAL INOCULATION | REMARKS |
|---|---|---|---|---|---|
| Boeck, 1905, (18) | Boeck's sarcoid; nasal mucosa | | | + | Slowly progressing tuberculosis in guinea pig |
| Kyrle, 1910, (104, 106) | Boeck's sarcoid; skin | | | + | Death of guinea pig after 10 months |
| Schlagenhaufer, quoted by Kyrle, 1914, (105) | Boeck's sarcoid; lymph nodes and spleen | | − | + | Death of guinea pig after 10 months |
| Kyrle, 1921, (107) | Boeck's sarcoid; skin | + | | | Only during early phase (about within the first three weeks) |
| Morawetz, 1910, (135) | Boeck's sarcoid; skin | | | + | Guinea pig died after 10 months |
| Volk, 1913, (206) | Darier-Roussy; subcutaneous nodule | | | + | |
| Jüngling, 1919, (87) | Cystic bone lesion—bone marrow | | | + | Guinea pig died after 6 months |
| Gans, 1921, (52) | Lupus pernio; skin | | | + | Slowly progressing tuberculosis in guinea pig |
| Ruete, 1922, (174) | Boeck's sarcoid; skin | + | | | In ten-day old focus |
| Krupnikoff, 1927, (99) | Boeck's sarcoid; skin | + | | | Only in fresh infiltration; rods not entirely typical in tinctorial reaction |
| *Hudelo, *et al.*, 1926, (quoted by Kissmeyer (92)) | Lupus pernio | + | | + | |
| Ravault, *et al.*, 1929, (165) | Boeck's sarcoid; skin | | | + | Two out of six guinea pigs showed acid-fast rods in lymph nodes, but no gross lesions |
| Watanabe & Mariyama, 1930, (212) | Boeck's sarcoid; skin | + | | − | |
| Dittrich, 1931, (39) | Boeck's sarcoid; skin | + | | | |
| Dittrich, 1931, (39) | Lupus pernio; skin | + | | | |

| | | | | | |
|---|---|---|---|---|---|
| Ramel, 1934, (164) | Lupus pernio; skin | | | + | On third animal transfer typical tuberculosis; culture from lesion: acid-fast bacilli slightly pathogenic for rabbits |
| Chatellier (quoted by Kissmeyer (92)) | "Atypical skin lesion" | | | + | Guinea pig on second animal passage developed local lesion at site of injection only. No growth obtained. (Original report not located) |
| Schaumann (quoted by Kissmeyer (92)) | Cystic bone lesions | | | + | Guinea pig died after 7 months. Patient had pulmonary tuberculosis. (Original report not located) |
| van Alstyne, 1933, (1) | Cystic bone lesion | + | | | |
| Ramel, 1934, (162) | Boeck's sarcoid; skin | | | + | Atypical tuberculosis in first guinea pig; on further animal transfer typical tuberculosis. Patient had tubercle bacilli in urine |
| Gougerot, 1934, (61) | | | | + | (Original report not available) |
| Sannicandro, 1934, (178) | Boeck's sarcoid; skin | | + | + | Patient had pyopneumothorax |
| Stalmann, 1934, (194) | Cystic bone lesion | | | + | Several guinea pigs developed slowly progressing tuberculosis |
| Chisholm, 1935, (29) | Cystic bone lesion | + | | | |
| Pautrier & Glasser, 1936, (155) | Boeck's sarcoid; skin | | | + | Rabbit developed atypical local lesion with caseation and acid-fast bacilli |

* This is apparently an erroneous reference. I have not been able to find the report in the place cited by Kissmeyer.

impressive. Kissmeyer stated in 1932 that he had found in the literature 39 cases of Boeck's disease in which animal inoculation was done and that 7 of them had given what seemed to be positive results. Since then many more attempts have been reported, most of them with negative results.

In table 2 I have summarized all positive bacteriological findings that I was able to find in the literature. The number of positive results is very small; the number of completely convincing positive results is insignificant. Practically all positive animal inoculations are represented by extremely slowly progressive disease or by atypical findings, such as strictly localized lesions, or tuberculous manifestations occurring only after animal passage. For this reason, critics question the reliability of these findings and suggest the likelihood of spontaneous infection. All these arguments are inconclusive, since the original authors often omit the description that could identify an inoculation tuberculosis.

In addition to positive inoculation experiments, some of which are probably beyond criticism, a number of authors have demonstrated acid-fast bacilli in tissue sections. Of these studies, Kyrle's observations (107) are of particular significance and present probably the explanation both for the positive and negative findings. Kyrle, as mentioned in the section *Histology* examined repeated biopsies from a patient with acute exacerbations of cutaneous carcoid. During the early inflammatory phase, many acid-fast bacilli were seen ten days after the onset; eleven days later only a few acid-fast bacilli were seen while the typical sarcoid structures had made their appearance; in later biopsies no acid-fast bacilli were seen.

During one of the febrile prodromal phases, Kyrle injected 5 cc. of blood into a guinea pig and into another one simultaneously bioptic skin material; the first guinea pig developed tuberculosis, the second did not. Kyrle concludes from this experiment that the bacilli are killed promptly in the skin. In the light of these observations it seems likely that tubercle bacilli may be present in sarcoid lesions only during the earliest phases of their development. This assumption is somewhat supported by Lewandowsky's experimental work which led him to the conclusion that freely propagating tubercle bacilli cause inflammatory lesions and that, where they are decomposed by the antibacterial factors of the host, granulomata, that is tubercles or tuberculoid structures, develop.

At the present state of our knowledge it would probably not serve any

useful purpose to attempt a further critical analysis of the positive findings assembled in table 2.

### *Haematology*

The blood picture does not show any changes that are constant or characteristic enough to help in the diagnosis. For a special study of the blood picture see Chevallier and Ely (27). That polycythaemia, due to the secondary pulmonary fibrosis, may occur, has already been mentioned. In many, but not in all cases, a moderate and sometimes high monocytosis is observed (31, 92, 103, 117, 119, 123, 130, 150, 151, 154, 163, 183). Since the monocytosis is obviously the haemotological manifestation of a monocytic proliferation leading to the epithelioid granulomata, it can be expected to occur only during the actively proliferating phase, hence the irregularity of this phenomenon.

### *Tuberculin Reaction*

In the majority of patients with sarcoid the tuberculin reaction is negative, or there exists a low degree of allergy (2, 6, 7, 9, 14, 92, 103, 104, 114, 115, 116, 117, 154, 162, 175). Martenstein (123) states that, of 82 patients with Boeck's sarcoid on whom tuberculin tests were done, 73 per cent gave a negative reaction, and 62 per cent of 46 patients with lupus pernio. Lomholt (115) reports 72 cases of Boeck's sarcoid with a negative Pirquet, 8 with a $\pm$, 18 with a $+$ and 2 with a $++$ reaction. This anergy plays an important rôle in aetiological discussions, as will be mentioned later.

### *Associated Lesions*

Equally important in regard to the aetiology and interpretation, are the combinations with other disease manifestations that have been observed. It is difficult, or probably impossible, to decide what features should be classed as manifestations of sarcoid itself and which ones should be considered as actual combinations. Without an attempt at such differentiation some of the more significant features are as follows: iridocyclitis (9, 10, 59, 77, 117, 130, 162, 175, 176, 192, 214); parotic swelling, sometimes suggestive of uveoparotid fever (6, 10, 59, 92, 93, 114, 117, 192, 196, 198); swelling of lachrymal glands, at times suggestive of Mikulicz syndrome (59, 79, 92, 93, 94, 117). Some form of tuberculosis, coëxisting with sarcoid, preceding or following it, is reported in

approximately 10 per cent of the cases. It seems to be the rule that the cutaneous manifestations—and at times others as well—heal spontaneously and rapidly when frank tuberculosis develops. This phenomenon has been emphasized particularly by Schaumann (186, 190), but it has been reported, too, by Goldschmidt, by Bonnevi and With, and by Strümpke. In a case of subcutaneous sarcoid of the Darier-Roussy type, Proppe saw the development of lupus vulgaris in the scar from the excision of the first lesion after three years.

### OSTITIS TUBERCULOSEA MULTIPLEX CYSTOIDES

These bone lesions, occurring most frequently in the phalanges and metacarpal and metatarsal bones, were first described as a separate clinical entity by Jüngling (87) in 1919 (4 cases) and in a more extensive paper (88) (9 cases) in 1928. It is evident that these lesions are but one of the possible manifestations of Boeck's sarcoid. As mentioned in the section on Boeck's sarcoid, these cyst-like bone lesions are demonstrable in many patients with Boeck's sarcoid and lupus pernio. In his second paper, Jüngling states that they were found in 29 out of 30 patients with lupus pernio that had been examined roentgenologically, but he stresses the fact that bone lesions may exist without skin lesions. This is apparently true of any localization of sarcoid lesions. Jüngling described the histological picture as a noncaseating tuberculosis, consisting chiefly of epithelioid cells, few giant cells and no necrosis. In only one case did he get a positive animal inoculation with biopsy material.

The type of bone lesion described by Jüngling was reported probably first in 1904 by Kreibich in two out of three patients with lupus pernio. Bloch (13) described another patient with lupus pernio, in 1907, in whom two metacarpal bones showed *spina-ventosa-like* lesions. In 1910, Rieder (169) made a report of 2 cases with the "combination of chronic osteomyelitis (*spina ventosa*) with lupus pernio."

Fraenkel observed a young man with enlarged spleen and multiple adenopathy; biopsy of lymph nodes showed purely fibrous tubercles, containing Langhans giant cells without any caseation. Practically all phalanges of both feet and some of the hands showed cyst-like lesions that Fraenkel called *spina ventosa multiplex adultorum* and interpreted as a peculiar form of multiple bone tuberculosis. It is interesting to note that this patient developed bilateral tuberculous iritis a few years later.

Detailed roentgenological descriptions of the bone lesions have been published by Jüngling, Fleischner who suggested the change from Jüngling's original *cystica* to *cystoides*, by Kirklin and Morton, Nielsen, and Heyden.

However, far more of these bone lesions are reported as part of the several clinical pictures of Boeck's sarcoid and related lesions than as separate entities.

The histological description given by Jüngling has been confirmed and completed mainly by Schaumann (183). He showed that in the bone marrow, just as in other localizations, one regressive development is fibrosis. He found the sarcoid lesions in bones that did not present any clinical disease nor roentgenological signs.

Similar to other sarcoid lesions, tubercle bacilli have only rarely been demonstrated. Van Alstyne and Gowen could demonstrate acid-fast rods in biopsy material from a case that was probably not entirely characteristic, since lesions were demonstrated in some of the long bones, and since there was some caseation histologically. Jüngling (88), Stalmann, and Chisholm demonstrated tubercle bacilli, the former two by animal inoculation, the latter bacterioscopically (see table 2).

Since Jüngling's disease is, as stated above, the osseous manifestation of Boeck's sarcoid and, as such, is so frequently associated with the latter, it appears entirely unnecessary to discuss in detail the further characteristics of this disease. There is again the frequent tuberculin anergy, frequency of monocytosis, chronicity, paucity of symptoms, and the same associated manifestations as discussed in greater detail under Boeck's sarcoid, for example, association with lupus vulgaris (Koch).

In addition to the papers mentioned above, the following ones seem to be of special interest for a more detailed account of *ostitis tuberculosea multiplex cystoides:* Hecht, Mayr, Doub and Menagh, Sanes and Smith, and Chevallier and Fiehrer (26).

### UVEOPAROTID FEVER

The clinical syndrome, first clearly described and differentiated from mumps by Heerfordt in 1909, is fairly rare. Some of the literature reviews are indicative of the frequency. Berg reviewed 40 cases in 1923, Roenne about 30 in 1928, Garland and Thomson (54) 47 in 1933, Savin 66 in 1934, Cohen and Rabinowitz about 65 in 1935, Nowkirischki about 70 in 1935, Folger about 60 cases in 1936, and Waldenström about 84 in 1937.

### *Histology*

In a number of cases biopsies were performed on the iris, the parotis or an associated lymph node. Lehmann, Atland (quoted by Garland and Thomson), Bang, Fleischer, Coppez (quoted by Garland and Thomson), and Ohno (quoted by Waldenström) examined pieces of iris and found a more or less typical tuberculous structure without caseation. Biopsies from the parotis were examined by Garland (53), Cavara, Haferkorn, Waldenström, Gram, Reimers, Weve, Cashell, and Slot, *et al.* All these authors agree that the histological character is that of tuberculosis without caseation. The lesions show usually many giant cells within the epithelioid proliferation, some marginal lymphocytes and fibrosis. Haferkorn and Slot, *et al.* observed some caseation. Waldenström seems to be the only observer who has removed biopsy material from an involved parotis twice with an interval of about 7 months. The first biopsy, taken during the clinically active phase of the disease, showed typical tubercles without caseation, the second showed massive sclerosis and shrinkage of the tissue with round cell infiltration.

The lymph nodes most frequently enlarged during the course of this disease are the hilar, cervical and supraclavicular. Kruskal and Levitt, and Cohen and Rabinowitz examined supraclavicular lymph nodes and Lehmann cervical lymph nodes; these authors found epithelioid cell tubercles, with a variable number of giant cells and no caseation.

Weve examined a biopsy from a swollen lachrymal gland in addition to one of parotis; both glands showed epithelioid cell tubercles. These bioptic findings are confirmed by necroptic observations.

### *Autopsies*

Bang reports the autopsy of a boy, who died about one year following the onset of the disease. Clinically there was bilateral iritis, bilateral parotitis, dacryoadenitis, peripheral lymphadenitis and massive enlargement of the hilar lymph nodes; later on exudative pleuritis developed. The autopsy showed miliary tuberculosis in pleurae, pericardium and peritoneum, massive caseous tuberculosis of the lungs, liver, spleen and brain. The lachrymal and sublingual glands showed a few epithelioid cell tubercles and much interstitial inflammation.

Souter had a patient with the characteristic signs of the disease who died 10 months after the onset. This patient, 40 years old, showed massive tuberculous involvement of the myocardium and the hilar lymph

nodes, miliary tuberculosis of pleurae and lungs. Thomson, who made a special report of the findings in the heart of this case, states that neither the myocardial focus nor the miliary tubercles in the lungs showed any evidence of caseation. All these lesions consisted mainly of epithelioid cells, some giant cells and few collagenous fibres.

Garland and Thomson (54) autopsied a woman, 28 years of age, who died with increasing dyspnoea and cyanosis about 5 months following the onset of her disease. The parotic glands were small and densely fibrosed. Dense miliary tubercles were scattered throughout the lungs, epicardium, peritoneum and kidneys. There was massive involvement of the myocardium without gross caseation and old caseated and calcified foci in the mesenteric lymph nodes. Microscopically all the miliary tubercles showed a structure characteristic of tuberculosis, but caseation was absent.

### *Bacteriology*

There seem to be only four positive bacteriological findings reported although numerous authors have attempted to demonstrate tubercle bacilli in the lesions. Cavara observed the development of a typical but chronic inoculation tuberculosis in one guinea pig out of several injected with biopsy material from the parotis.

In the case reported by Souter and by Thomson, tubercle bacilli were found bacterioscopically in the "triturated" material from the myocardial focus.

Tanner and McCurry found typical appearing acid-fast bacilli in histological sections from the parotis gland in their case 2. (This is apparently the same case as the one mentioned by McCurry in the discussion of Savin's paper (179).)

According to Slot, *et al.*, van der Hoeve demonstrated acid-fast rods in a preauricular lymph node.

### *Associated Lesions*

*Lung:* In many cases of uveoparotid fever, intrathoracic lesions are reported of the same main character as those in Boeck's sarcoid. They are either enlargements of the hilar lymph nodes or scattered parenchymal lesions, or both, in most cases again distinguished by the paucity of signs and symptoms. Such roentgenological findings are reported by Souter, confirmed by autopsy findings, Tanner and McCurry (two cases), Savin, Garland (53), Cohen and Rabinowitz, Haferkorn, Gram, Reimers,

Kruskal and Levitt, Garland and Thomson (54) (this case had a normal chest roentgenogram early in the disease but showed productive miliary tubercles in the lungs at autopsy), Davies, Müller, Nowkirischki, Rieth, Schall, Levin and Slot, *et al.*

*Skin:* Erythema nodosum or erythematous lesions highly suggestive of this diagnosis were observed by Brewerton, Cohen and Rabinowitz, Davies, Merrill and Oaks, Levin, Gram, and Waldenström.

*Lachrymal glands:* In a number of cases the lachrymal glands were enlarged. Cavara and Weve proved the histological identity of the involvement. In other cases, the involvement of the lachrymal glands was so marked, or there was associated enlargement of the submaxillary and sublingual glands that a clinical syndrome similar to or identical with Mikulicz' disease was evident in addition to uveoparotid fever. Such cases were reported by Bang (2 cases), Berg, Hamburger and Schaffer whose paper is entitled "Uveoparotid fever as a manifestation of Mikulicz's syndrome." Reed describes a case of an 18 year old boy who had a crop of flat healing ulcers on the back, swollen cervical lymph nodes, chronic parotitis, and enlargement of the other salivary glands uveitis, but no apparent involvement of the lachrymal glands; histologically cervical lymph nodes showed fibrosis, but no tubercles. A case of "polyneuritis preceded by inflammation of the parotid, lachrymal and mammary glands" (173) may be mentioned in this connection.

*Tuberculosis:* Frank tuberculosis or lesions strongly suggestive of tuberculosis are found in a considerable percentage of patients, as are tuberculous antecedents. Garland (53) biopsied tuberculids in one patient and found typical productive tubercles. Merrill and Oaks, and Levin report pleural effusions, the former during the illness, the latter preceding it.

*Sarcoid:* Kruskal and Levitt found typical sarcoid lesions in a cervical lymph node and Bering reported a case of Boeck's sarcoid with typical histological findings, complicated by uveoparotic fever. Slot, *et al.* observed and discuss in some detail the coëxistence of uveoparotid fever and cutaneous sarcoid lesions.

*Bones:* Kuhlefeldt reports signs and symptoms suggestive of *ostitis tuberculosea multiplex cystoides* in a patient with uveoparotid fever, but no X-ray films of the involved limbs were made. Since many cases of this bone lesion are unsuspected without roentgenological examination and since roentgenological examinations of the small bones are not reported in these patients, it is quite possible that bone cysts character-

istic of noncaseating tuberculosis might be found in a considerable percentage of patients with uveoparotid fever if their small bones were regularly X-rayed.

### *Tuberculin Reaction*

Tuberculin anergy exists in the majority of cases. Failure to react to an intracutaneous injection of 1 mgm. Old Tuberculin or more is reported by Levin, Kruskal and Levitt, Hamburger and Schaffer, Cohen and Rabinowitz, and Waldenström. Negative reactions to smaller or not specified amounts of tuberculin were seen by Garland and Thomson (54), Savin, Souter, Weve, Thomson, Mohr, Mackay, Leeksma, Nowkirischki, Cavara, Brewerton, and Slot, *et al.* I have not found any attempts to demonstrate anticutins or procutins in patients with uveoparotid fever.

### *Haematology*

In a number of cases, monocytosis, similar to that in Boeck's sarcoid, is reported (Tanner and McCurry, Folger, Hamburger and Schaffer). But since blood counts are not reported in many cases, it is impossible to state how frequently monocytosis actually occurs.

## UNCLASSIFIED CASES OF NONCASEATING TUBERCULOSIS

It has been mentioned repeatedly that lesions with sarcoid structure may invade practically any organ of the body, that they may produce a widespread involvement or that they may occur in single organs only. However, apparent confinement to one particular organ may in many cases be simply a matter of demonstrability. Without roentgenological examination, most cystic bone lesions, mediastinal lymph node involvement and pulmonary lesions would never be detected. Other lesions remain unsuspected until revealed by necropsy. Lesions that present the characteristic histological structure of sarcoid have been observed in various organs and, because of unusual location or symptoms and signs caused by the particular localizations, have been described under a number of different names. Some cases belonging to this motley group are related here.

In the cases listed below, it must be assumed that in many of them additional lesions might have been present, but were not detectable by the diagnostic procedures employed.

According to different organ systems, the following case reports are

cited to complete further the clinical and anatomical manifestations that probably belong in the field of noncaseating tuberculosis.

*Lung:* These cases, at least some of their important representatives, have been mentioned under Boeck's sarcoid. Special reference is made here to cases described as chronic miliary tuberculosis, *miliaris discreta* and *granulie froide.* It is particularly doubtful whether in such cases of a diffuse miliary seeding other organs are not involved; but, since in the cases mentioned autopsies were not done, the question remains open. However, in other cases (Nonnenbruch, Hantschmann) clinical evidence of a more universal involvement is present in the form of bone cysts, skin lesions, enlarged spleen and lymph nodes. It is probably significant that all autopsied cases with pulmonary dissemination showed numerous extrapulmonary foci as well.

*Lymph nodes:* Cases with noncaseating lesions in multiple groups of lymph nodes have been reported by Chiari, Walz, Mylius and Schürmann, and Schürmann (2 cases.)

*Spleen:* A number of cases with strictly proliferative, noncaseating lesions in the spleen have been reported, for example by Jadassohn (84), Lubarsch, Engelbreth-Holm (4 cases), Leidel whose case had, however, enlarged axillary lymph nodes that were not examined histologically. Carling and Hicks reported two cases of tuberculous splenomegaly with noncaseating lesions; their first case came to autopsy and showed, in addition to the splenic lesions, miliary involvement of lungs, liver and lymph nodes; this case belongs, accordingly, to the next group. Their second case, in which only the excised spleen was examined pathologically, did not show any clinical evidence of other localizations.

*Generalized forms:* Chiari autopsied a patient with massive enlargement of hilar and other lymph nodes. Histologically, the lesions consisted of epithelioid cell tubercles with giant cells and fibrosis; only a few foci showed minimal caseation. In the main lesion in the hilar nodes, neither caseation nor tubercle bacilli could be found, but bacilli were demonstrated in some of the other foci. Askanazy described a case with miliary tubercles in spleen, bone marrow and all lymph nodes, none showing caseation; this patient had up to 20 per cent monocytes during his illness. Askanazy refers to two similar cases in the literature. In the antiformin-digested spleen acid-fast rods were found. Gebsattel reported a case with involvement of practically all lymph nodes, spleen, liver, lung, all consisting of epithelioid tubercles with much fibrosis and without caseation. Esser studied, under the name of atypical tuber-

culosis, two cases that belong in this category. Waetzold reported one case with involvement of lungs and multiple lymph nodes. Mylius and Schürmann (138), in addition to the case of pure lymph node involvement, observed and autopsied a second patient with massive involvement of the lymph nodes in the pulmonary and hepatic hilum, of small bones, iris and skin. Histologically all lesions were identical with those described by Schaumann, showing the various stages of pure epithelioid cell tubercles to fibroma-like sclerosed nodules. Only the foci in the lungs showed caseation. These authors advocate for this form of tuberculosis the term universal, sclerosing tuberculous large cell hyperplasia.

Clinical observations without autopsy reports of apparently noncaseating generalized tuberculosis are reported by Hantschmann, Nonnenbruch, Bödeker and Freund.

### MIKULICZ'S SYNDROME

Mikulicz described a "peculiar symmetrical disease of the lachrymal and salivary glands" first in a brief case presentation in 1888 and in a detailed report in 1892. The cases that Mikulicz had seen himself and clinically similar cases from the literature made it quite obvious that the syndrome is not causes by *one* single aetiological agent. One of Mikulicz's cases was probably due to tuberculosis: "the main mass of the 10 times enlarged lachrymal gland consists of granulation tissue; in this are found numerous typical tubercles with Langhan's giant cells." There is no indication in this brief description of the presence or absence of caseation, but it permits probably of the conclusion that Mikulicz's syndrome *can* be caused by tuberculosis.

Later observations confirmed both these points, that Mikulicz's syndrome has no uniform aetiology and that one of its possible aetiological agents is tuberculosis.

We are here not concerned with the totality of this syndrome, but only with those relatively rare cases that seem to belong in the group of noncaseating tuberculosis. For a comprehensive discussion of Mikulicz's syndrome, irrespective of aetiology, the reader is referred to Meller, Howard, Schaffer and Jacobsen.

It is purely an artificial division to separate cases showing the complete syndrome and cases that have only symmetrical involvement of the lachrymal glands without swelling of the salivary glands. Such an incomplete case was reported by van Duyse in 1896; the lachrymal gland lesion is described as tuberculous tissue, consisting chiefly of epithelioid

and giant cells with practically no regressive changes, with very few leucocytes and without demonstrable tubercle bacilli. According to van Duyse, similar cases had been reported by Abadie, de Lapersonne, Müller, Baas and Salzer; only in Müller's two cases were acid-fast bacilli demonstrated. These latter cases lead over to frank tuberculosis of the lachrymal glands with typical caseation and acid-fast bacilli, such as the cases reported by Plitt and Napp. Another "incomplete" case, showing bilateral swelling of the lacyrimal glands, followed later by involvement of submaxillary glands, was reported by Igersheimer and Pöllot; this patient did not react to 5 mgm. Old Tuberculin; biopsy material injected into a guinea pig and rabbit did not produce tuberculosis, and showed histologically epithelioid cell tubercles without caseation. On the other hand, de Jong and Joseph reported *un cas fruste de syndrome de Mikulicz* with involvement of all salivary glands, but without disease of the lachrymal glands; since this case had chronic iritis and conjunctivitis, it might as well be assigned to uveoparotid fever as to an incomplete Mikulicz's syndrome.

The following authors report cases that are definitely tuberculous or highly suggestive: Osler, his patient died of pulmonary tuberculosis; Stieren, his patient had marked supraclavicular lymphadenitis and signs of pulmonary tuberculosis; Fleischer, his patient had in addition to the complete syndrome a peculiar conjunctivitis, enlargement of the spleen and peripheral lymph nodes; excised pieces from the conjunctiva showed epithelioid cell tubercles with few giant cells which Baumgarten did not hesitate to call tuberculosis in spite of the absence of acid-fast bacilli in the sections. Meller reported one case associated with lupus vulgaris; Krailsheimer a case of Mikulicz's syndrome with peripheral lymphadenitis and tubercles in the right iris, the excised submaxillary gland showing chronic interstitial inflammation with giant cells and many acid-fast bacilli; Detzel, a case with the characteristic picture of noncaseating, sclerosing tuberculosis. The case reported by Reed belongs probably more closely to uveoparotid fever than to Mikulicz's syndrome, since his patient had, in addition to swelling of the salivary glands, uveitis, but no involvement of the lachrymal glands.

Quite a few cases are on record in which biopsy of the involved glands show either simple lymphocytic infiltration or a nonspecific fibrosis. It is possible, but not provable, that such findings, particularly in cases showing fibrosis (Hirsch), represent late stages of noncaseating tuberculosis.

The chief arguments for assuming that *some* cases of Mikulicz's syndrome are noncaseating tuberculosis, are: their histological characteristics, with or without demonstrable tubercle bacilli, and the cases that stand somewhere in between the typical syndrome and other clinical pictures, uveoparotid fever in particular, that we assume to belong to the field of noncaseating tuberculosis.

It is unfortunate for the purpose of the present discussion that, in most of the case reports of Mikulicz's syndrome, scant attention is given to the examination beyond the obviously involved parts. Roentgenograms of the chest and bones, tuberculin tests and blood counts are reported all too infrequently in these patients. It would appear quite likely that more thorough examinations would reveal in a certain number of these patients pulmonary and hilar involvement, cystic bone lesions, tuberculin anergy, monocytosis—in brief, those phenomena that are apparently characteristic of noncaseating tuberculosis.

## DISCUSSION

The main contention of this review is that the various clinical pictures discussed belong in the uniform aetiological and morphological group, noncaseating tuberculosis. This contention implies the postulate that these various clinical pictures comprise a definite entity, that they belong together in a more than casual manner, that they are really only different manifestations of the same morbid process. Disregarding for the moment their aetiology, the evidence should be briefly reviewed that justifies the assumption of their essential identity.

Probably the most important evidence is the uniform histology of the lesions whose unit is the epithelioid tubercle without caseation and with its potential developments as discussed. The next point is the overwhelming frequency of tuberculin anergy. But, from the clinical and diagnostic point of view, their identity is best shown by those features that they have in common and by the relative frequency of overlapping clinical manifestations.

The features common to this group of clinical pictures are: (*1*) the disseminated pulmonary lesions and tracheobronchial lymph node enlargement, (*2*) peripheral lymphadenopathies, (*3*) cystic bone lesions, (*4*) chronicity, (*5*) paucity of symptoms, and (*6*) monocytosis during the active stage. It would be repetitious to cite again the great frequency of these features. Indeed, the question whether a given case is reported as Boeck's sarcoid with pulmonary and ocular lesions, or as disseminated

pulmonary tuberculosis with iritis, or as Jüngling's disease with skin and eye lesions, or as uveoparotid fever with intrathoracic foci and sarcoid skin lesions, seems often to depend simply on the question of whether the report is made by a dermatologist, an internist, a roentgenologist, or an ophthalmologist. From the clinical-roentgenological point of view the similarity or identity of the intrathoracic lesions in all these clinical pictures is particularly impressive.

While the occurrence of the characteristic lesions in the three systems, lungs, lymph nodes and bones, has a high diagnostic value, and while additional lesions in salivary glands, skin and in the uveal tract designate the traditional clinical pigeon hole to which a given case may be assigned, it must be remembered that many cases are "incomplete" and that often the proper diagnosis will be missed if one is not prepared to recognize partial manifestations of a traditional syndrome.

The overlapping of clinical features in cases showing manifestations that belong to more than one of the established clinical entities is a further significant indication of the real unity of these conditions. The review of cases mentioned must have made it clear that the exact definition of the traditional clinical pictures has become somewhat arbitrary. Typically Boeck's sarcoid may be taken to include involvement of skin and lymph nodes; Jüngling's disease, involvement of small bones; uveoparotid fever, involvement of parotic glands and uveal tract; and Mikulicz's syndrome, involvement of salivary and lachrymal glands. However, the incidence of Jüngling's disease in Boeck's sarcoid is probably as frequent as the incidence of Boeck's sarcoid in Jüngling's disease. Iritis is reported in many cases of Boeck's sarcoid (see references above), so is the involvement of salivary glands, and so is the involvement of lachrymal glands. Iritis associated with Mikulicz's syndrome is reported (Gjessing, Reed), lachrymal gland involvement in uveoparotid fever (Cavara, Mohr, Weve). Berg emphasizes the overlapping of Mikulicz's syndrome and uveoparotid fever. Jackson, reviewing the relationship of uveoparotid fever and Mikulicz's syndrome, states editorially: "It would appear that the syndromes described by Mikulicz and Heerfordt have important points in common." In brief, all possible combinations between the classical pictures of Boeck's sarcoid (inclusive of lupus pernio and Darrier-Roussy's sarcoids), uveoparotid fever, Jüngling's disease and Mikulicz's syndrome occur, and the types of cases mentioned under "unclassified cases of noncaseating tuberculosis" add further variety and significant links to the possible combinations.

That all these clinical pictures are noncaseating tuberculosis is meant to apply, *in toto*, to Boeck's sarcoid and its closely related skin lesions, such as lupus pernio, Darrier-Roussy's subcutaneous sarcoid, angiolupoid, to *ostitis tuberculosea multiplex cystoides*, to the sarcoid lesions of internal organs, particularly the lungs, described as Boeck's sarcoid, Schaumann's benign lymphogranulomatosis, or the so called universal sclerosing large cell tuberculous hyperplasia, and to uveoparotid fever. It is possible that a few exceptional cases presenting these syndromes may be caused by other agents. But Mikulicz's syndrome is obviously not an aetiological entity, and it has been pointed out above which of the cases on record are most likely to be noncaseating tuberculosis.

The proof of the tuberculous aetiology rests on a number of arguments. The strict bacteriological proof is available for so few cases that it is not convincing by mere numbers. However, there appear to be good reasons why bacilli are so rarely found. In Boeck's sarcoid which may well be considered the type lesion of the entire group, Kyrle has been able to show that bacilli are present only during a brief initial phase. The particular immunological situation that determines the morphological characteristics of the lesions may well be the cause for the prompt killing of bacilli.

Not much value can be attached to the finding of tubercle bacilli in the sputum of patients with sarcoid (Keck, Schaumann (184)), since it is impossible to know in what phase of the disease the pulmonary lesions were.

The sarcoid tubercle must be considered the extreme representative of the productive reaction in tuberculosis. It is well known that in undoubted tuberculous foci bacilli are increasingly difficult to demonstrate the more the productive reaction predominates.

Keeping this general behavior in mind, the few positive bacteriological findings done at the correct time assume an importance that far exceeds the frequency of the occurrence.

The next argument in favor of the tuberculous aetiology is the morphological nature of the lesions. This particular phase of the tuberculous tissue reaction has probably first been described by Ziegler in his textbook under the name of "large cell hyperplasia." He says that "the large-celled tissue here and there is transformed after a while into a homogenous hyaline mass or into a mass composed of glistening flakes (Schollen)." This is the sclerotic process described above. It is difficult to think of an aetiological agent that would cause a histological picture that is apparently so characteristic for *one* phase of tuberculosis, with the

globular arrangement of epithelioid cells, the Langhans giant cells and the typical developments of fibrosis, resorption and, in few instances, caseation.

This developmental relation between sarcoid lesion and frank, caseating, bacilliferous tuberculosis is the next and very powerful argument in the present contention. This relation must be viewed from two angles: (*1*) a transformation of sarcoid lesion into classical tuberculosis, and (*2*) the apparent mutual exclusiveness of sarcoid and classical tuberculosis. As to the former, it may be recalled that four autopsied cases of Boeck's sarcoid died of frank tuberculosis, one other case showed miliary tubercles in the peritoneum, and another one bilateral hydrothorax. In the four cases with frank tuberculosis, it was the definite impression of the observers that there was a gradual transformation of sarcoid lesions into caseated foci. The three autopsied cases of uveoparotid fever all had apparently generalized tuberculosis.

Autopsy reports of cases of Jüngling's disease *per se* are not available; but patients with the characteristic lesions are among the autopsy cases of Boeck's sarcoid.

The mutual exclusiveness between sarcoid and caseous tuberculosis presents two aspects. In some cases, lesions in one organ system retrogress as lesions in another organ system evolve, a phenomenon that is not any too rare in tuberculosis. The other aspect of this problem is apparently contained in the fact that sarcoid lesions exist and persist precisely in the immunological milieu that is incompatible with caseous tuberculosis, that is, anergy. But this is a purely speculative matter about which some more will be said in connection with the prevailing immunological factors.

It might seem paradoxical to adduce tuberculin anergy as an argument in favor of tuberculous aetiology. However, the failure to react to tuberculin is so frequent in these patients that a mere coincidence is entirely out of the question. It is not only the frequency of anergy that implies that these nonreactors cannot all be free from infection with tubercle bacilli, but the not infrequent antecedents of tuberculous disease provide positive proof.

It might, then, be assumed that sarcoidal lesions exert an anergizing influence upon their bearers, similar to measles for example. But this is rather unlikely because such anergizing action, be it through intercurrent disease or through experimentally induced desentization, is usually of brief duration, and it can be shown that it is only a quantita-

tive depression of tuberculin allergy and not a complete extinction. In sarcoid, however, the anergy is often complete, as attested by many cases that did not react to 1 mgm. of tuberculin or more. The anergy appears, therefore, to be an essential feature of the disease, significantly related to its aetiology. This impression is further confirmed by the demonstration that patients with sarcoid lesions and with tuberculin anergy have substances in their blood serum that react specifically with tuberculin, enhancing or neutralizing the skin reactivity of tuberculin (Martenstein, 122, 123, Goldschmidt, Sulzberger). The demonstration of these so called procutins and anticutins has been done in an insufficient number of patients to permit a definite conclusion as to the regularity of their occurrence and their possible causal relationship to anergy. This topic is probably a fruitful field for further investigation of the relationship between anergy and the peculiar morphology of the sarcoid reaction.

If, for the sake of argument, the close association of anergy, specific serum properties and absence of caseation be assumed, with the unquestioned corollary of the association between allergy and caseation, the question still remains why some patients present this triad and most of them do not.

One might look for the answer in the nature of the invading bacillus. The available evidence would indicate that tubercle bacilli isolated from sarcoid are of low virulence for experimental animals; nevertheless, some produced caseating lesions. And some patients with Boeck's sarcoid and with uveoparatod fever died of progressive tuberculosis, presumably caused by the same strain that caused the preceding noncaseating phase.

That the answer is more likely to be found in the host than in the parasite is suggested by the observation that some patients react to nonspecific stimuli (india ink) with the formation of sarcoid structure (Volk (207)). Oppenheim found the same response following injections of morphine. Volk suggests that some individuals, either on account of their particular immunological or constitutional situation, are endowed with the "sarcoidal form of reaction."

It is a highly suggestive observation that rats form sarcoid-like lesions following the injection of tubercle bacilli, that they do not develop tuberculin allergy after infection and that their serum contains tuberculin neutralizing substances that behave like anticutins (W. Jadassohn (85)). As Jadassohn emphasizes, the triad, absence of caseation, anergy and anticutins, is realized in the experimental tuberculosis of

rats the same as in human sarcoid. Gloyne and Page, too, found that rats reacted with the formation of epithelioid cell tubercles without caseation and without sensitization to tuberculin. The rat is the extreme example of the purely productive reaction to tubercle bacilli. Nieberle (142, 143), in his studies on spontaneous animal tuberculosis, stresses the fact that certain species show a more or less purely productive reaction. According to this author, the primary reaction of the horse is the local proliferation of histiocytes, a "primary productive reaction," leading in the advanced stages to a diffusely infiltrating large-celled granulation tissue, essentially without regressive changes. A similar productive reaction is the rule in dogs; here, Nieberle stresses the absence of polymorphonuclear leucocytes, the preponderance of epithelioid cells and the minimal caseation. Similar findings are reported in cats. But the preponderance of purely productive processes is particularly clear in foxes and related species. Little is known about the tuberculin reactivity in these animal species. Gerlach, however, mentions that 33 to 40 per cent of tuberculous dogs do not react to tuberculin.

The fact that different animal species differ in just those biological and morphological characteristics that distinguish sarcoid from classical tuberculosis suggests strongly that the factor or factors determining the sarcoid reaction are to be looked for in the host rather than in the parasite.

Summarizing, it might be said that the arguments in favor of the tuberculous aetiology of the clinical pictures discussed are:

(*1*) Demonstration of tubercle bacilli
(*2*) Histological character
(*3*) Transformation into classical tuberculosis
(*4*) Tuberculin anergy
(*5*) Disappearance of sarcoid lesions with the development of frank tuberculosis
(*6*) Serological data (anticutins and procutins)
(*7*) Simultaneous or successive occurrence of lesions definitely or probably tuberculous
(*8*) The close similarity between sarcoid reactions in humans and in certain animal species

It is not the intention of this study to discuss the various opinions on the aetiology of any or all the diseases mentioned. Suffice it to say that a number of prominent workers believe that tuberculosis is not the aetiological agent (Kissmeyer, Longcope, Nichols, Hunter, Pautrier,

Zieler). Kissmeyer believes that Boeck's sarcoid is caused by a specific microörganism that stands probably somewhere between the tubercle bacillus and the leprosy bacillus. Rabello advocates the idea that sarcoid is a manifestation of leprosy itself. This opinion, which is based essentially on the similarity of certain cutaneous manifestations and does not take into account the systemic feature of the disease, has found little favor and definite opposition by Reenstierna and Wade. Darier (36) is the main representative of the opinion that sarcoid is a uniform reaction of the body against a multiplicity of possible stimuli, of which the tubercle bacillus, possibly in its filterable form, is one. The opinion that tuberculosis is the aetiological agent is held by Schaumann, Bloch, Jadassohn, Goeckerman, Volk, Martenstein, Montgomery, and many others. The evidence in favor of the tubercle bacillus as an aetiological agent of uveoparotid fever is most ably and emphatically presented by Garland and Thomson.

Various more or less definite attempts to define the field of a noncaseating or purely productive form of tuberculosis and to include more or less the diseases mentioned in this paper have been made by Mylius and Schürmann (who do not include uveoparotid fever and Mikulicz's syndrome), by Pagel, by Slot, *et al.* and more fully by Waldenström.

In describing this group of clinical syndromes, pointing out their aetiological similarities and assembling the evidence for the assumption that they are noncaseating tuberculosis, the latter term should not be understood as a separate *type of tuberculosis*, but rather as a *phase of tuberculosis*. While the chronicity and the stability of the lesions attest to the potential long duration of this phase, the rarely occurring transformation into caseating forms proves its temporary character. Similar to the lack of stability of the lesions in time one must recognize equally the fact that the characteristic "noncaseating" is not an absolute definition of its nature. Repeated reference has been made to lesions showing minimal caseation; this could be amplified by cases showing all the clinical essentials of noncaseating tuberculosis, but revealing histologically well marked areas of caseation, such, for example, as the cases reported by Jacobsen, Katzenstein, Vastine and Bacon, and Schaumann. For the proper classification of border-line cases it is well to remember that definitions are arbitrary divisions without necessarily strictly parallel phenomena in reality and that pathological terminology must be based, and generally is based, on Virchow's principle: *e fortiori denominatio fit.* But just such border-line cases provide probably a most

important clue for the proper understanding and accurate aetiological classification.

In other words, while noncaseating tuberculosis should be recognized as a fairly well defined entity despite its polymorphous manifestations, it should be clearly understood that there is no rigid dividing line between noncaseating and caseating phases; the typical representatives are clear cut and easily recognizable, but transformation from the former to the latter and border-line cases occur occasionally.

The particular conditions that favor development and persistence of noncaseating lesions are insufficiently understood. Without going into the interesting but highly speculative discussions of Jadassohn (83), Lewandowsky (113), Volk (207) and others on the interdependence of immunobiological factors and morphological characteristics, actual observation indicates that failure to react to tuberculin is commonly associated with the noncaseating phases of tuberculosis. Whether this anergy is cause or effect, whether it is dependent on the infecting strain, on constitutional or on immunological particularities of the host, or on the modalities of the apparently chronic intermittent haemotogenous dissemination, all these questions must wait for further studies to be solved.

## SUMMARY

1. The available literature is analyzed in an attempt to show that Boeck's sarcoid and related lesions, *ostitis tuberculosea multiplex cystoides*, uveoparotid fever, certain cases of Mikulicz's syndrome and a motley group of unclassified cases, are manifestations of noncaseating tuberculosis.

2. Noncaseating tuberculosis is a particular phase of tuberculosis that is characterized by (*a*) its strictly productive lesions, (*b*) repeated haemotogenous seedings, (*c*) its particular affinity to lung, lymphoid tissue, small bones, glands, and the uveal tract, (*d*) its discrepancy between marked anatomical involvement and paucity of symptoms, (*e*) its relative chronicity, and (*f*) by its marked tendency to tuberculin anergy.

## BIBLIOGRAPHY

(1) VAN ALSTYNE, G. H., AND GOWEN, H.: Osteitis tuberculosea mutiplex cystoides, Jour. Bone & Joint Surg., 1933, *19*, 193.

(2) ALTMANN, K.: Zur Kenntnis der Boeck'schen Erkrankung, Arch. f. Derm., 1921, *135*, 1.

(3) ASKANAZY, M.: Über lupöse Tuberkulose des Blutbildungsapparat und tuberkulöse Splenomegalie, Beitr. path. Anat., 1927, *69*, 563.

(4) Assman, H.: Die akute und chronische Miliartuberkulose der Lungen, Ztschr. Tuberk., 1927, *47*, 485.
(5) Bang, S.: Quoted by Garland and Thompson.
(6) Barmwater: Über Boeck's Sarkoid auf den Schleimhäuten, Hals-Arzt, 1936, *27*, 259.
(7) Beintema, K.: Quelques observations concernant les sarcoïdes de Boeck, Bull. Soc. Franç. derm., 1934, *41*, 1112.
(8) Berg, F.: Über Febris uveo-parotidea, Zentrbl. f. Ophthal., 1924, *13*, 254.
(9) Bergel, A., and Scharff, O.: Zur internen Klinik des Boeck'schen Miliarlupoids, Wien. klin. Wchnschr., 1933, *46*, 1224.
(10) Bering, F.: Zur Kenntnis des Boeck'schen Sarkoids, Derm. Ztschr., 1910, *17*, 404.
(11) Bernstein, M., Konzlemann, F., and Sidlick, D.: Boeck's sarcoid, Arch. Int. Med., 1929, *44*, 721.
(12) Besnier, E.: Lupus pernio de la face, Ann. de derm., 1889, *10*, 333.
(13) Bloch, B.: Beitrag zur Kenntnis des Lupus pernio, Mon. hefte f. prakt. Derm., 1907, *45*, 177.
(14) Bloch, B.: Boeck's Sarcoid mit Beteiligung der Knochen und der Schleimhaut des harten Gaumens, Cor. bl. f. Schweiz. Ärzte, 1916, *46*, 275.
(15) Bödeker, F.: Über eine gutartige Form der disseminierten Lungentuberkulose. (Tuberkulide der Lungen), Med. Klin., 1932, *28*, 929.
(16) Boeck, C.: Multiple benign sarcoid of the skin, Jour. Cut. & Genito-Ur. Dis., 1899, *17*, 543.
(17) Boeck, C.: Weitere Beobachtungen über das multiple benigne Sarkoid der Haut, Arch. f. Derm., Festschrift f. Kaposi, 1900, p. 153.
(18) Boeck, C.: Fortgesetzte Untersuchungen über das multiple benigne Sarkoid, Arch. f. Derm., 1905, *73*, 71.
(19) Bonnevie, P., and With, T.: Ein Fall von Sarkoid Boeck, Ibid., 1937, *175*, 407.
(20) Brewerton, E. W.: Bilateral parotitis and cyclitis, Trans. Ophthal. Soc. Un. Kingd., 1910, *30*, 148.
(21) Brocq, L., and Pautrier, L. M.: L'angio-lupoide, Ann. de derm., 1913, *4*, 1.
(22) Burman, M. S., and Mayer, L.: Arthroscopic examination of the knee joint, Arch. Surg., 1936, *32*, 846.
(23) Carling, E. R., and Hicks, A. B.: Two cases of tuberculous splenomegaly, Brit. Med. Jour., 1925, *2*, 291.
(24) Cashell, G. T. W.: A case of uveoparotid tuberculosis, Royal Berkshire Hosp. Rep., 1934–5, p. 77.
(25) Cavara, V.: Sopra un caso di febris uveo-parotidea subchronica di Heerfordt, Bollettino d'oculistica, 1928, *7*, 925.
(26) Chevallier, P., and Fiehrer, A.: La polydactylite pseudokystique pure (ou polyostéite nodulaire pseudokystique primitive des extrémités), Bull. Soc. Franç. derm., 1934, *41*, 1144.
(27) Chevallier, P., and Ely, Z.: Les formules sanguines du lupus pernio, de l'érythème induré de Bazin et des sarcoïdes, Ibid., 1934, *41*, 1228.
(28) Chiari, O. M.: Über einen Fall ausgedehnter Lymphdrüsentuberkulose, Wien. klin. Wchnschr., 1911, *24*, 523.
(29) Chisholm, D. R.: A case of osteitis tuberculosea multiplex cystica, Canad. Med. Assn. Jour., 1935, *32*, 302.
(30) Cohen, S. J., and Rabinowitz, M. A.: Uveoparotitis, Jour. Amer. Med. Assn., 1935, *105*, 496.
(31) Courmont, P., Gaté, J., Gardère, H., and Müller: Maladie de Besnier-Boeck, Bull. Soc. Franç. derm., 1936, *43*, 834.

(32) Danbolt, N., and Hval, E.: Le sarcoide (lupoide) de Boeck, Acta Derm.-Ven., 1936, *17*, 477.
(33) Darier, J.: Die kutanen und subkutanen Sarkoide, Mon. schr. f. prakt. Derm., 1910, *50*, 419.
(34) Darier, J.: Sur la nature et la pathogénie des tuberculides et sarcoïdes, Schweiz. med. Wchnschr., 1929, *10*, 1209.
(35) Darier, J.: Les tuberculides devraient être appelées "Tuberculoides", Bull. Soc. Franç. derm., 1932, *30*, 112.
(36) Darier, J.: Considérations sur la nature des sarcoïdes, Ibid., 1934, *41*, 999.
(37) Davies, T. A. L.: Uveo-parotitis polyneuritica, Lancet, 1934, *227*, 746.
(38) Detzel, L.: Ein Beitrag zur Beziehung der Mikulicz'schen Erkrankung zur Tuberkulose der Tränendrüsen, Klin. Mon. bl. f. Augenh., 1917, *59*, 381.
(39) Dittrich, O.: Über den direkten Tuberkelbazillen-Nachweis bei Lupus pernio und bei Sarkoid Boeck, Derm. Ztschr., 1931, *60*, 395.
(40) Doub, H. P., and Menagh, F. R.: Bone lesions in sarcoid: A roentgen and clinical study, Amer. Jour. Roentgen., 1929, *21*, 149.
(41) van Duyse: Tuberculose atténuée des glands lacrymales, Arch. d'ophthalm., 1896, *16*, 554.
(42) Ehrmann: Die Tuberkulide, Arch. f. Derm., 1914, *119*, 83.
(43) Engelbreth-Holm, J.: A study of tuberculous splenomegaly and splenogenic controlling of the cell emission from the bone marrow, Amer. Jour. Med. Sc., 1938, *195*, 32.
(44) Ernsting, H. C.: Boeck's sarcoid with coëxisting Darier-Roussy's sarcoid, Arch. Ophthal., 1937, *17*, 493.
(45) Esser, A.: Beiträge zur Frage der atypischen Tuberkulose, Beitr. Klin. Tuberk., 1926, *64*, 76.
(46) Fleischer, B.: Ein Fall von eigentümlicher symmetrischer Thränen-und Ohrspeicheldrüsenschwellung mit Erkrankung der Conjunctiva, Klin. Mon. bl. f. Augenh., 1902, *40*, 398.
(47) Fleischner, F.: Die Erkrankung der Knochen bei Lupus pernio und Boeck's Miliarlupoid. (Ostitis tuberculosea mutiplex cystoides, Jüngling), Fortschr. Geb. Roentgenstr., 1924, *32*, 193.
(48) Folger, H. P.: Uveoparotitis (Heerfordt), Arch. Ophthal., 1936, *15*, 1098.
(49) Fraenkel, E.: Über eine eigenartige Form multipler Knochentuberkulose. (Spina ventosa adultorum), Beitr. Klin. Tuberk., 1922, *50*, 441.
(50) Freund, E.: Über universelle sklerosierende tuberkulöse grosszellige Hyperplasie, Ztschr. Tuberk., 1932, *64*, 339.
(51) Funk, C. F.: Boeck'sches Sarkoid, Lupus pernio und Lungenbeteiligung, Arch. f. Derm., 1933, *167*, 560.
(52) Gans, O.: Über Lupus pernio und seine Beziehungen zum Sarkoid Boeck, Derm. Ztschr., 1921, *33*, 64.
(53) Garland, H. G.: Uveo-parotid tuberculosis, Lancet, 1934, *227*, 743.
(54) Garland, H. G., and Thomson, J. G.: Uveo-parotid tuberculosis, Quart. Jour. Med., 1933, *2*, 157.
(55) Gebsattel, v. E.: Beitrag zum Verständnis atypischer Tuberkuloseformen, Beitr. Klin. Tuberk., 1919, *43*, 1.
(56) Gerlach, F.: Die allergische Diagnostik der Tuberkulose in der Veterinärmedizin, Ergebn. d. allg. Pathol., 1931, *25*, 813.
(57) Gjessing, H. G. A.: Über Iridocyclitis als Teilerscheinung bei der Mikulicz'schen Erkrankung, Klin. Mon. bl. f. Augenh., 1916, *56*, 254.

(58) GLOYNE, S. R., AND PAGE, D. S.: The reaction to B. tuberculosis in the albino rat, Jour. Path. & Bact., 1923, *26*, 224.
(59) GOECKERMAN, W. H.: Sarcoid and related lesions, Arch. Derm., 1928, *18*, 237.
(60) GOLDSCHMIDT, W. N.: Über circinär-verrucöse Umwandlung bei einem Sarkoid Boeck und eine ähnliche Form bei Lupus vulgaris, Arch. f. Derm., 1925, *149*, 331.
(61) GOUGEROT, H.: Sarcoides, Bull. Soc. Franç. derm., 1934, *41*, 1017.
(62) GRAM, F.: Uveoparotid tuberculosis, Lancet, 1936, *231*, 245.
(63) GRSCHEBIN, S.: Concerning the identity of sarcoid Boeck, sarcoids Darier-Roussy, erythyma induratum, Bazin and lupus pernio, Urol. & Cut. Rev., 1935, *39*, 477.
(64) HAFERKORN, M.: Zur Kenntnis des Heerfordt'schen Symptomen-komplexes, Mon. schr. f. Kinderh., 1935, *63*, 161.
(65) HAMBURGER, L. P., AND SCHAFFER, A. J.: Uveoparotid fever as a manifestation of mikulicz's syndrome, Amer. Jour. Dis. Child., 1928, *36*, 434.
(66) HANSEMANN, v. D.: Die Lymphangitis reticularis der Lungen als selbständige Erkrankung, Virchow's Arch., 1915, *220*, 311.
(67) HANTSCHMANN, L.: Über torpide Formen disseminierter Tuberkulose, Beitr. Klin. Tuberk., 1930, *73*, 688.
(68) HECHT, P.: Über spezifische Lungenerkrankung bei Lupus pernio und Ostitis tuberculosea multiplex cystica, Ztschr. Tuberk., 1928, *51*, 125.
(69) HEERFORDT, C. F.: Uber eine "Febris uveo-parotidea subchronica" an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paresen cerebrospinaler Nerven kompliziert, Arch. f. Ophthal., 1909, *70*, 254.
(70) HELD, A.: Die chronische Miliartuberkulose der Lungen und ihre Beziehung zu Ranke's Lehre, Fortschr. Geb. Roentgenstr., 1931, *43*, 703.
(71) HELD: Die epitheloidzellige Tuberkulose der Lungen, Roentgenpraxis, 1931, *3*, 927.
(72) HEYDEN, W.: Die Ostitis tuberculosea multiplex cystoides und die tuberkuloiden Gewebsveränderungen anderer Organsysteme, Beitr. Klin. Tuberk., 1935, *86*, 23.
(73) HIRSCH, C.: Ein weiterer Beitrag zur Lehre von der symmetrischen Erkrankung der Thränen—und Mundspeicheldrüsen (Mikulicz), Mitt. Grenzgeb. Med. Chir., 1898, *3*, 381.
(74) HOWARD, C. P.: Mikulicz's disease and allied conditions, Internat. Clin., 1909, *1*, 30.
(75) HUDELO, MONTLAUR AND LAFORESTIER: Lymphogranulatomatose de Schaumann, cited by KISSMEYER (92).
(76) HUDELO, L., AND RABUT, R.: Le sarco-lupus pernio, Bull. Soc. Franç. derm., 1934, *41*, 1109.
(77) HUSEN, v. J.: Ein Beitrag zur Kenntnis des Boeck'schen Miliarlupoids, Derm. Ztschr., 1919, *28*, 1.
(78) HUNTER, F. T.: Hutchinson-Boeck's disease (Generalized "Sarcoidosis"), New England Jour. Med., 1936, *214*, 346.
(79) HVIDT, C.: Remarks on Boeck's sarcoid, with special reference to its occurrence on mucous membranes, Acta Oto-Laryng., 1923, *5*, 87.
(80) IGERSHEIMER, J., AND PÖLLOT: Über die Beziehungen der Mikulicz'schen Krankheit zur Tuberkulose, Arch. f. Ophthal., 1910, *74*, 411.
(81) JACKSON, S.: Mikulicz's disease and uveoparotitis, (editorial), Amer. Jour. Ophthal., 1935, *18*, 469.
(82) JACOBSEN, A. W.: Generalized tuberculosis of the lymph nodes and multiple cystic tuberculosis of the bones, Jour. Pediatr., 1936, *8*, 292.
(83) JADASSOHN: Die Tuberkulide, Arch. f. Derm., 1914, *119*, 10.
(84) JADASSOHN: Zur Frage der "Sarcoide," des Lupus pernio und des Lupus miliaris, Cor. bl. f. Schweiz. Ärzte, 1919, *49*, 455.

(85) JADASSOHN, W.: L'origine tuberculeuse de la maladie de Boeck, Bull. Soc. Franç. derm., 1934, *41*, 1344.
(86) DE JONG, S. J., AND JOSEPH, H.: Un cas fruste de syndrome de Mikulicz chez un infantile, Bull. et mêm. Soc. méd. d'hôp. Paris, 1908, *25*, 140.
(87) JÜNGLING, O.: Ostitis tuberculosea multiplex cystica, Fortschr. Geb. Roentgenstr., 1919, *27*, 375.
(88) JÜNGLING, O.: Über Ostitis tuberculosea multiplex cystoides, Beitr. klin. Chir., 1928, *143*, 401.
(89) KATZENSTEIN, G.: Beitrag zur Klinik der generalisierten Drüsentuberkulose und der Ostitis tuberculosea multiplex cystoides, Zentrbl. f. inn. Med., 1935, *56*, 561.
(90) KECK, A.: Untersuchungen über einen Tuberkelbazillenstamm aus der Lunge einer Patientin mit Boeck's Sarcoid, Derm. Wchnschr., 1925, *80*, 429.
(91) KIRKLIN, B. R., AND MORTON, S. A.: Roentgenologic changes in sarcoid and related lesions, Radiol., 1931, *16*, 328.
(92) KISSMEYER, A.: La maladie de Boeck, Copenhagen, 1932.
(93) KISSMEYER, A.: Contribution à l'étude clinique des sarcoïdes, Bull. Soc. Franç. derm., 1934, *41*, 1102.
(94) KISSMEYER, A.: Contribution à l'étude anatomo-pathologique des sarcoïdes, Ibid., 1934, *41*, 1278.
(95) KISSMEYER, A., AND NIELSEN, J.: Notes sur l'étiologie des sarcoïdes de Boeck, Acta Derm., 1933, *14*, 283.
(96) KOCH, F.: Über Ostitis tuberculosea multiplex cystoides, Derm. Wchnschr., 1935, *101*, 919.
(97) KRAILSCHEIMER: A case of Mikulicz's disease with pronounced tubercle of the iris, Ophthalmoscope, 1908, *6*, 172.
(98) KREIBICH, K.: Über Lupus pernio, Arch. f. Derm., 1904, *71*, 3.
(99) KRUPNIKOFF, D.: Zur Ätiologie des Boeck'schen Sarkoid, Derm. Wchnschr., 1927, *84*, 165.
(100) KRUSKAL, I. D., AND LEVITT, J. M.: Uveoparotid tuberculosis, Amer. Jour. Ophthal., 1935, *18*, 735.
(101) KUHLEFELDT, E.: A case of subchronic febrile uveo-parotid inflammation, Brit. Jour. Ophthal., 1917, *1*, 621.
(102) KUZNITZKY: Lungenveränderungen bei Boeck's Sarkoid, resp. Lupus pernio, Fortschr. Geb. Roentgenstr., 1920, *27*, 563.
(103) KUZNITZKY, E., AND BITTORF, A.: Boeck'sches Sarkoid mit Beteiligung innerer Organe, München. med. Wchnschr., 1915, *62*, 1349.
(104) KYRLE, J.: Über eigentümliche histologische Bilder bei Hauttuberkulose und deren Beziehung zum benignen Miliarlupoid (Boeck), Arch. f. Derm., 1910, *100*, 375.
(105) KYRLE, J.: Zur Frage des Boeck'schen Lupoids, Ibid., 1914, *119*, 117.
(106) KYRLE, J.: Über die tuberkuloiden Gewebsstrukturen der Haut, Ibid., 1917, *125*, 481.
(107) KYRLE, J.: Die Anfangsstadien des Boeck'schen Sarkoids; Beitrag zur Frage der Ätiologie dieser Dermatose, Ibid., 1921, *131*, 33.
(108) LEEKSMA, H. W.: Quoted by GARLAND AND THOMPSON.
(109) LEHMANN, K.: Quoted by GARLAND AND THOMPSON.
(110) LEIDEL, G.: Ein Beitrag zur tuberkulösen Splenomegalie, Centrl. bl. f. allg. Path. u. path. Anat., 1930, *48*, 54.
(111) LENARTOWITZ, J., AND ROTHFELD, J.: Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirn und den inneren Organen, Arch. f. Derm., 1930, *161*, 504.
(112) LEVIN, P. H.: The neurological aspects of uveo-parotid, Jour. Nerv. & Ment. Dis., 1935, *81*, 176.

(113) LEWANDOWSKY, F.: Die Tuberkulose der Haut, Berlin, 1916.
(114) LEWANDOSWKY, F.: Zur Kenntnis der Boeck'schen Sarkoide, Arch. f. Derm., 1921, *135*, 287.
(115) LOMHOLT, S.: Sur les lésions muqueuses dans les sarcoïdes, Bull. Soc. Franç. derm., 1934, *41*, 1142.
(116) LOMHOLT, S.: Zwei Fälle von Sarcoid Boeck mit eigentümlichen grossen circinären Infiltraten in der Haut, Arch. f. Derm., 1936, *174*, 132.
(117) LONGCOPE, W. T., AND PIERSON, J. W.: Boeck's sarcoid (sarcoidosis), Bull. Johns Hopkins Hosp., 1937, *60*, 223.
(118) LUBARSCH, O.: Pathologische Anatomie der Milz, Lubarsch-Henke Handb., vol. *1*, part 2, p. 373.
(119) LUTZ, W.: Zur Kenntnis des Boeck'schen Miliarlupoids, Arch. f. Derm., 1919, *126*, 947.
(120) MACKAY, G.: A case of uveo-parotitis with irido-cyclopegia, Brit. Jour. Ophthal., 1917, *1*, 612.
(121) MALONEY, E. R., AND COMBES, F. C.: Darier-Roussy's sarcoid, Arch. Derm. & Syph., 1936, *33*, 709.
(122) MARTENSTEIN, H.: Wirkung des Serums von Sarkoid-Boeck und Lupus pernio Kranken auf Tuberkulin, Arch. f. Derm., 1921, *136*, 317.
(123) MARTENSTEIN, H.: Sarkoid Boeck and Lupus pernio, Ibid., 1924, *147*, 70.
(124) MAUSS: Ein Fall von Boeck'schem Sarcoid, Ztschr. f. Laryngol., 1933, *24*, 222.
(125) MAYR, J. K.: Zur Kasuistik des Lupus pernio mit Knochenveränderungen, Arch. f. Derm., 1928, *155*, 248.
(126) MAZZA, G.: Über das multiple benigne Sarkoid der Haut, Ibid., 1908, *91*, 57.
(127) MELLER, J.: Über die Beziehungen der Mikulicz'schen Erkrankung zu den lymphomatösen und chronisch entzündlichen Prozessen, Klin. Mon. bl. f. Augenh., 1906, *44*, 177.
(128) MERRILL, H. G., AND OAKS, L. W.: Uveoparotitis (Heerfordt), Amer. Jour. Ophthal., 1931, *14*, 15.
(129) MICHALIK, R.: Zur Kasuistik des Boeck'schen Sarkoids, Derm. Wchnschr., 1924, *78*, 445.
(130) MICHELSEN, J.: Zur Frage des Boeck'schen Sarkoids, einer besonderen Form der Tuberkulose, Deutsche med. Wchnschr., 1931, *57*, 574.
(131) MIKULICZ, v. J.: Über eine eigenartige symmetrische Erkrankung der Thränen-und Mundspeicheldrüsen, Beitr. z. Chir., Festschr. f. Theodor Billroth, 1892, p. 610.
(132) MOHN, A.: Ein Fall von Febris uveo-parotidea, Acta Ophthal., 1933, *11*, 397.
(133) MOHR, T.: Ein Fall von Iridocyclitis mit gleichzeitiger chronischer Parotisschwellung, Klin. Mon. bl. f. Augenh., 1920, *64*, 694.
(143) MONTGOMERY, H.: Histopathology of various types of cutaneous tuberculosis, Arch. Dermat., 1937, *35*, 698.
(135) MORAWETZ, G.: Miliarlupoid (Boeck), Arch. f. Derm., 1910, *99*, 457.
(136) MÜLLER, M.: Bemerkungen zu der Arbeit von H. Rieth., Klin. Mon. bl. f. Augenh., 1920, *64*, 387.
(137) MYLIUS, K.: Boeck'sches Sarkoid und Auge, Ztschr. f. Augenh., 1920, *65*, 71.
(138) MYLIUS, K., AND SCHÜRMANN: Universelle sklerosierende tuberkulöse grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose, Beitr. Klin. Tuberk., 1930, *73*, 166.
(139) NAPP, O.: Über die Beziehung der Mikulicz'schen Krankheit zur Tuberkulose, Ztschr. f. Augenh., 1907, *17*, 513.
(140) NICHOLAS, J., AND GATÉ, J.: Apropos des sarcoïdes, Bull. Soc. Franç. derm., 1934, *41*, 1011.

(141) NICKERSON, D. A.: Boeck's sarcoid, Arch. Path., 1937, *24*, 19.
(142) NIEBERLE, K.: Pathologische Anatomie und Pathogenese, Ergebn. d. allg. Path., 1931, *25*, 630.
(143) NIEBERLE, K.: D. Tuberkulose der Fleischfresser und Affen, Ibid., 1932, *26*, 711.
(144) NIELSEN, J.: Recherches radiologiques sur les lésions des os et des poumons dans les sarcoïdes de Boeck, Bull. Soc. Franç. derm., 1934, *41*, 1187.
(145) NONNENBRUCH, W.: Über eine besondere Form von gutartiger chronischer Lungentuberkulose, Deutsche med. Wchnschr., 1931, *57*, 919.
(146) NOWKIRISCHKI, A. D.: Über einen Fall von Febris uveo-parotidea, Klin. Mon. bl. f. Augenh., 1935, *95*, 620.
(147) OPPENHEIM, M.: Knoten-und Strangbildung nach Morphiuminjektionen (Pseudosarkoid), Arch. f. Derm., 1922, *137*, 74.
(148) OSLER, W.: On chronic symmetrical enlargement of the salivary and lachrymal glands, Amer. Jour. Med. Sc., 1898, *115*, 27.
(149) PAGEL, W.: Pathologische Anatomie der hämatogenen Streuungstuberkulose, Ergebn. ges. Tuberkfg., 1933, *5*, 266.
(150) PAUTRIER, L. M.: Sarcoides de Boeck généraliseés, Bull. Soc. Franç. derm., 1933, *40*, 1540.
(151) PAUTRIER, L. M.: Cinq cas de maladie de Besnier-Boeck, Ibid., 1934, *41*, 1054.
(152) PAUTRIER, L. M.: Les lésions granuliques pulmonaires de la maladie de Besnier-Boeck, Bull. et Mém. Soc. Méd. d'hôp. Paris, 1934, *50*, 1409.
(153) PAUTRIER, L. M.: La maladie de Besnier-Boeck, Presse méd., 1935, *43*, 146.
(154) PAUTRIER, L. M.: Les lésions érythrodermiques pures de la maladie de Besnier-Boeck-Schaumann, Ann. de derm., 1936, *7*, 433.
(155) PAUTRIER, L. M., AND GLASSER, R.: Inoculation positive probable au lapin, au point d'inoculation, de lésions de maladie de Besnier-Boeck-Schaumann, Bull. Soc. Franc. derm., 1936, *43*, 505.
(156) PINNER, M.: Hematogenous (non-miliary) pulmonary tuberculosis, Amer. Jour. Roentgen., 1934, *31*, 442.
(157) PINNER, M.: Boeck's disease. Postmortem findings in a case with visceral lesions, Amer. Jour. Path., 1937, *13*, 674.
(157a) PINNER, M.: Noncaseating tuberculosis, Amer. Rev. Tuberc., 1937, *36*, 706.
(158) PLANCHEREL, C.: Beitrag zur Lehre vom Boeck'schen Sarkoid, Derm. Ztschr., 1914, *21*, 676.
(159) PLITT, W.: Über Tuberkulose der Tränendrüsen, Beil. heft klin. Mon. bl. f. Augenh., 1905, *43*, 40.
(160) PROPPE, A.: Zur Frage des Darier-Roussy'schen Sarkoids, Derm. Ztschr., 1936, *72*, 311.
(161) RABELLO, J.: Données nouvelles pour l'interprétation de l'affection de Besnier-Boeck rôle de la lèpre, Ann. de derm., 1936, *7*, 571.
(162) RAMEL, E.: Syndrome de Besnier-Boeck, Bull. Soc. Franç. derm., 1934, *41*, 1122.
(163) RAMEL, E.: Association d'angio-lupoïdes et de sarcoïdes dermiques de type Boeck, Ibid., 1934, *41*, 1134.
(164) RAMEL, E.: D'un lupus pernio (type Schaumann), probablement déterminé par un bacille tuberculeux de type bovin, Ibid., 1934, *41*, 1332.
(165) RAVAUT, P., VALTIS, J., AND NÉLIS, P.: Résultats de l'inoculation au cobaye d'un sarcoide et d'une tuberculide papulo-nécrotique, Compt. rend. Soc. de biol., 1929, *101*, 444.
(166) REED, W. E.: Mikulicz's syndrome in association with tuberculosis, Lancet, 1934, *227*, 749.
(167) REENSTIERNA, J.: The possible rôle of leprosy in the etiology of the Besnier-Boeck Sarcoid and Schaumann's syndrome, Internat. Jour. Leprosy, 1937, *5*, 433.

(168) REIMERS, O.: Über einen Fall von Febris uveo-parotidea und über die Beziehungen zur Tuberkulose, Ztschr. f. Augenh., 1926, *60*, 30.
(169) RIEDER, H.: Über Kombination von chronischer Osteomyelitis (Spina ventosa) mit lupus pernio, Fortschr. Geb. Roentgenster., 1910, *15*, 125.
(170) RIETH, H.: Iridocyclitis bei Parotitis epidemica, Klin. Mon. bl. f. Augenh., 1919, *63*, 527.
(171) RISCHIN, M.: Universelles benignes Miliarlupoid Boeck mit Beteiligung innerer Organe, Arch. f. Derm., 1922, *139*, 30.
(172) ROENNE: Über Febris uveo-parotidea, Klin. bl. f. Augenh., 1928, *81*, 524.
(173) ROGERS, B., AND BODMAN, H. J.: Polyneuritis preceded by inflammation of the parotid, lachrymal and mammary glands, Bristol Med. Chir. Jour., 1926, *43*, 84.
(174) RUETE, A.: Zur Aetiologie der Boeck'schen Erkrankung, Derm. Ztschr., 1922, *37*, 129.
(175) SAACKE, M.: Ein Beitrag zur Frage der Lungenveränderungen bei Boeck'schem Sarcoid, Med. Welt., 1936, *10*, 124.
(176) SALVESEN, H. A.: The sarcoid of Boeck, a disease of importance to internal medicine, Acta Med. Scand., 1935, *86*, 127.
(177) SANES, S., AND SMITH, W. S.: Osteitis tuberculosa multiplex cystica of fibula and tibia, Jour. Amer. Med. Assn., 1934, *102*, 1206.
(178) SANNICANDRO, G.: Allgemeine sarkoide Hauttuberkulose, Derm. Ztschr., 1934, *69*, 305.
(179) SAVIN, S. H.: An analysis of the signs and symptoms of 66 published cases of the uveoparotid syndrome, with details of an additional case, Trans. Ophthal. Soc. Un. Kingd., 1934, *54*, 549.
(180) SCHAFFER, A. J., AND JACOBSEN, A. W.: Mikulicz's syndrome, Amer. Jour. Dis. Child., 1927, *34*, 327.
(181) SCHALL, E.: Beitrag zur Aetiologie der Uveo-parotitis subchronica, Klin. Mon. bl. f. Augenh., 1923, *70*, 350.
(182) SCHAUMANN, J.: Étude sur le lupus pernio et ses rapports avec les sarcoides et la tuberculose, Ann. de derm., 1916, *6*, 357.
(183) SCHAUMANN, J.: Études histologiques et bactériologiques sur les manifestations médullaires de la lymphogranulomatose bénigne, Ibid., 1918, *7*, 385.
(184) SCHAUMANN, J.: Sur la nature du lymphogranulome bénign, Acta Derm.-Ven., 1921, *2*, 409.
(185) SCHAUMANN, J.: Démonstrations, Ibid., 1922, *3*, 428.
(186) SCHAUMANN, J.: Le lupus pernio et les sarcoïdes au point de vue étiologique, Ibid., 1922, *3*, 679.
(187) SCHAUMANN, J.: Étude anatomo-pathologique et histologique sur les localisations viscérales de la lymphogranulomatose bénigne, Bull. Soc. Franç. derm., 1933, *40*, 1167.
(188) SCHAUMANN, J.: Lymphogranulamatose bénigne sans manifestations cutanées, Ibid., 1933, *40*, 1793.
(189) SCHAUMANN, J.: Observations cliniques, bactériologiques et sérologiques pour servir à l'étiologie de la lymphogranulomatose bénigne, Ibid., 1934, *41*, 1296.
(190) SCHAUMANN, J.: Lymphogranulomatose benigna in the light of prolonged clinical observations and autopsy findings, Brit. Jour. Derm., 1936, *48*, 399.
(191) SCHÜRMANN: Zur Frage der Gesetzmässigkeiten in Ablauf der Tuberkulose unter besonderer Berücksichtigung der Entwicklungsganslehre Rankes, Beitr. path. Anat., 1929, *18*, 568.
(192) SLOT, W. J. B., GOEDBLOED, J., AND GOSLINGS, J.: Die Besnier-Boeck-(Schaumann-)-sche Krankheit und die Uveo-Parotitis (Heerfordt), Acta Med. Scand., 1938, *44*, 74.

(193) SOUTER, W. C.: A case of uveo-parotid fever with autopsy findings, Tr. Ophthal. Soc. Un. Kingd., 1929, *49*, 113.
(194) STALMANN, A.: Osteitis tuberculosea multiplex cystoides, Arch. klin. Chir., 1934, *178*, 669.
(195) STIEREN, E.: Tubercular dacryoadenitis and conjunctivitis, Bull. Johns Hopkins Hosp., 1901, *12*, 349.
(196) STRANDBERG, J.: Contribution à la question de la clinique et de la pathogénie de la sarcoïde de Boeck, Act. Derm.-Ven., 1921, *2*, 253.
(197) STRÜMPKE, G.: Boeck'sches Sarkoid bei ausgedehnter Allgemeintuberkulose, Derm. Ztschr., 1920, *20*, 199.
(198) SULZBERGER, M. B.: Sarcoid of Boeck and tuberculin allergy, Amer. Rev. Tuberc., 1933, *28*, 734.
(199) SUNDELIN, F.: Fall av benign miliarlupoids (Boeck), Hygiea, 1933, *95*, 481.
(200) TANNER, S. E., AND MCCURRY, A. L.: Uveo-parotid tuberculosis, Brit. Med. Jour., 1934, *2*, 1041.
(201) THOMSON, J. G.: An unusual case of diffuse tuberculous infiltration of the myocardium, Jour. Path. & Bact., 1930, *33*, 259.
(202) TILLGREN, J.: Diabetes insipidus as a symptom of Schaumann's disease, Brit. Jour. Derm. & Syph., 1935, *48*, 223.
(203) ULRICH, K.: Die Schleimhautveränderungen der oberen Luftwege bei Boeck's Sarcoid und ihre Stellung zum Lupus pernio, Arch. f. Laryngol., 1912, *31*, 506.
(204) VALENTINI, A.: Sull'aspetto radiologico delle lesioni polmonari nel sarcoide de Boeck, Radiol. med., 1928, *15*, 942.
(205) VASTINE, J. H., AND BACON, E. P.: Osteitis tuberculosea multiplex cystica, Radiol., 1935, *24*, 22.
(206) VOLK, R.: Zur Kenntnis der "subkutanen Sarkoide" (Darier-Roussy), Wien. klin. Wchnschr., 1913, *26*, 1425.
(207) VOLK, R.: Tuberkulose der Haut, in Jadassohn's Hndb. d. Haut u. Geschlechtskrankheiten, Berlin, 1931, vol. *10*, part 1.
(208) WADE, H. W.: Leprosy and sarcoid: Internat. Jour. Leprosy., 1937, *5*, 503.
(209) WAETZOLD: Quoted by PAGEL (149).
(210) WALDENSTRÖM, J.: Über gutartige, universelle, tuberkuloide Granulome mit besonderer Berücksichtigung der Uveoparotitis, Zbl. f. ges. Tub. fg., 1937, *45*, 249.
(211) WALZ: Indurierende Lymphdrüsentuberkulose des Mediastinums, Verh. deutsch. pathol. Ges., 1912, *15*, 78.
(212) WATANABE, K., AND MARIYAMA, G.: Zur Aetiologie des Miliarlupoids Boeck, Zentr. bl. f. Hautkrh., 1930, *31*, 90.
(213) WEINBERGER, F.: Boeck'sches Miliarlupoid und Tuberkulose, München. med. Wchnschr., 1916, *63*, 892.
(214) WEISSENBACH, R., LEHMANN, P., MARTINEAU, J., AND KAPLAN, M.: Forme ostéoganglionnaire de la maladie de Besnier-Boeck, Bull. Soc. Franç. derm., 1935, *42*, 253.
(215) WEVE: Familiäre Uveo-parotitis unbekannten Ursprungs, Klin. Mon. bl. f. Augenh., 1927, *78*, 83.
(216) ZIEGLER, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 2, Jena, 1906, p. 143.
(217) ZIELER, E.: Discussion to JADASSOHN.

# INDEX OF SUBJECTS AND AUTHORS


ADDINGTON, ERCELL A., AND SUTHERLAND, CHARLES G. Roentgenographic features of tuberculosis in bones and joints, 31

Age, Effect of, on the total pulmonary capacity and its subdivisions, 662

Aid to pneumothorax therapy, Positive intrapleural pressure as an, 542

ALLEN, E. H., AND CORNELY, PAUL B. Tuberculous infection in Negro colleges, 549

AMBERSON, J. BURNS, JR. Has tuberculosis treatment been effective? (editorial), 254

Antiserum, Intracutaneous reactions against, in tuberculosis, 238

ARNOLD, LLOYD, AND HIRSCHBERG, NELL. The effect of human tissue juices on tubercle bacilli, 598

Artery, pulmonary, Thrombosis of, 394

AUERBACH, OSCAR. The progressive primary complex, 346

Auxiliary techniques in chest roentgenography, 14

Avian tuberculosis, Studies in,

1. Avian tubercle bacilli in generalized disease in swine, 579
2. Comparative virulence of avian and bovine tubercle bacilli for rabbits and guinea pigs, 582
3. Sensitization method of differentiating avian from bovine infection in guinea pigs and rabbits, 588
4. The possible rôle of the avian tubercle bacillus in infection in man, 594

Bacillaemia, Tuberculous, in rabbits.

1. Bacillaemia in nonallergic animals, 507
2. Bacillaemia in allergic animals, 520

Bacilli, tubercle, Effect of human tissue juices on, 598

BERG, WILLIAM N. Statistical basis of errors in immunity tests, 259

Bilateral phrenic-nerve interruption in the treatment of pulmonary tuberculosis, 420

BLADY, JOHN V., AND COHEN, LOUIS. Fluoroscopy during pneumothorax treatment, 634

BLOCH, ROBERT G., FRANCIS, BYRON F., EISELE, C. WESLEY, AND MASON, ELWOOD W. Roentgenological group examinations for pulmonary tuberculosis, 174

Bones and joints, tuberculosis in, Roentgenographic features of, 31

BOOKS:

Cumulative index of the American Review of Tuberculosis, Volume I to Volume XXXIV, 104

PETERSEN, WILLIAM F. The patient and the weather, vol. IV, part 2, Organic disease (hypo and hyperthyroidism, diabetes, the blood dyscrasias, tuberculosis), 104

ALEXANDER, JOHN. The collapse therapy of pulmonary tuberculosis, 107

CORYLLOS, POL N. The surgery of pulmonary tuberculosis, 110

SWYNGHEDAUW, RAYMOND. Le moignon pulmonaire dans le pneumothorax thérapeutique, 112

LEVINSON, SAMUEL A., AND MACFATE, ROBERT P. Clinical laboratory diagnosis, 114

RAW, NATHAN. The control of bovine tuberculosis in man, 115

PARDO, I. J. Base para la interpretación de la radiografía del tóraxd el adulto. La imagen en el sujeto sano (proyeccion dorso-ventral), 116

FRIMANN-DAHL, J., AND WAALER, GEORG. Röntgenologische und pathologisch-anatomische Studien über den tuberkulösen Primärkomplex, 117

The Medical Committee of Air Hygiene Foundation of America, Inc., Medical Series, Bulletin No. 1. Silicosis and allied disorders, history and importance, 118

CANNAVÓ, LETTERIO. La broncospirochetosi di Castellani, 119

IZZO, ROQUE A., and others. Anales del Centro de Investigaciones Tisiologicas, 121

Health in colleges. Proceedings of the Second National Conference on College Hygiene, 121

Manual of tuberculosis for public health nurses. New York State Department of Health, Division of Public Health Nursing and Division of Tuberculosis, 122

CARLET, ANTONIA. Histoire des idées sur la guérison des cavernes depuis Laennec, 123

BACMEISTER, A. Die klimatische Behandlung der Tuberkulose und ihre heutige Bewertung, 123

ECOT, F. CH., AND JULLIEN, W. La thoracoplastie par voie axillaire, 124

KANTOR, JOHN L. Synopsis of digestive diseases, 124

LEMOINE, J.-M. La thrombose de l'artère bronchique cause de dilatation bronchique chronique de l'adulte, 124

BOYNTON, RUTH E., DIEHL, HAROLD S., AND SHEPARD, CHARLES E. The relative value of fluoroscopic, roentgenographic and physical examinations in a tuberculosis case-finding program in university students, 49

Bronchial factor in cavitation, 336

BROWN, ESTELLE W. See NELSON, WALDO E., *et al.*, 286, 311

Brown, Lawrason, 1871–1937, in memoriam, 361

Calcified intrathoracic lesions, Intracutaneous tuberculin reaction associated with, 311

Capacity, total pulmonary, and its subdivisions, Effect of age on the, 662

Case fatality rates in tuberculosis, Present trend of, 125

Case-finding program, tuberculosis, in university students, Relative value of fluoroscopic, roentgenographic and physical examinations in a, 49

Cases, new, Degree of tuberculosis in, 57

Cavitation, Bronchial factor in, 336

Cavity bearer, Prognosis of the, 65

Cervical lymph nodes, Tuberculosis of, 410

Changes, retrogressive, of tubercles, Studies on the, 484

CHARR, ROBERT, AND POU, JAIME F. Thrombosis of pulmonary artery, 394

Cheeks, Tuberculosis of the gums and, 381

Chest roentgenography, Auxiliary techniques in, 14

Chronic pulmonary disease, Functional test in, 369

Clinical versus the Public Health point of view in the treatment of tuberculosis, 533

Coagulation reaction, Weltmann serum, 200

COHEN, LOUIS, AND BLADY, JOHN V. Fluoroscopy during pneumothorax treatment, 634

COHEN, ROBERT V., AND WILLAUER, GEORGE. Bilateral phrenic-nerve interruption in the treatment of pulmonary tuberculosis, 420

Colleges, Negro, Tuberculous infection in, 549

Complex, primary, Progressive, 346

Control, Tuberculosis, 612

CORNELY, PAUL B., AND ALLEN, E. H. Tuberculous infection in Negro colleges, 549

CORPER, H. J., AND VIDAL, C. B. Intracutaneous reactions against antiserum in tuberculosis, 238

Course of experimental pneumococcus infection in tuberculous rabbits, 93

CRAWFORD, A. B. Studies in avian tuberculosis.

1. Avian tubercle bacilli in generalized disease in swine, 579
2. Comparative virulence of avian and bovine tubercle bacilli for rabbits and guinea pigs, 582
3. Sensitization method of differentiating avian from bovine infection in guinea pigs and rabbits, 588

4. The possible rôle of the avian tubercle bacillus in infection in man, 594

Daily variations in the tuberculin reaction.
1. The range of variation in tuberculous and control subjects, 264
2. Relation to the vascular pressor episode, 273

DAUER, C. C. Sex differences in tuberculosis mortality in the United States, 435

Degree of tuberculosis in new cases, 57

Diagnosis and treatment of tuberculous tracheobronchitis, 315

Diagnostic methods, roentgenological, Notes on the choice of, 1

DIEHL, HAROLD S. See BOYNTON, RUTH E., *et al.*, 49

Differences, Sex, in tuberculosis mortality in the United States, 435

Disease, pulmonary, chronic, Functional test in, 369

Dissemination, Tuberculous, during therapeutic pneumothorax, 494

DROLET, GODIAS J. Present trend of case fatality rates in tuberculosis, 125

DUCHAINE, JACQUES P. Tuberculous bacillaemia in rabbits.
1. Bacillaemia in nonallergic animals, 507
2. Bacillaemia in allergic animals, 520

EDITORIAL. Has tuberculosis treatment been effective?, 254

EDSALL, GEOFFREY. Positive intrapleural pressure as an aid to pneumothorax therapy, 542

Effect of age on the total pulmonary capacity and its subdivisions, 662

—— —— human tissue juices on tubercle bacilli, 598

EISELE, C. WESLEY. See BLOCH, ROBERT G., *et al.*, 174

ELLWART, LUCIA. See SALEY, D. H., *et al.*, 245

Errors in immunity tests, Statistical basis of, 259

Examination, sputum, Flotation method of, 525

Examinations, fluoroscopic, roentgenographic and physical, Relative value of, in a tuberculosis case-finding program in university students, 49

Examinations, group, Roentgenological, for pulmonary tuberculosis, 174

Experimental oleothorax, 245

—— pneumococcus infection in tuberculous rabbits, Course of, 93

—— tuberculosis, Influence of sunlight upon, 448

Extrapulmonary primary tuberculosis, Incidence of, 465

Factor, Bronchial, in cavitation, 336

Fatality rates in tuberculosis, case, Present trend of, 125

Features, Roentgenographic, of tuberculosis in bones and joints, 31

Fibrin bodies, Intrapleural, 81

FLAHIFF, E. W. A tuberculosis survey in Jamaica, 560

Flotation method of sputum examination, 525

Fluoroscopic, roentgenographic and physical examinations, Relative value of, in a tuberculosis case-finding program in university students, 49

Fluoroscopy during pneumothorax treatment, 634

FRANCIS, BYRON F. See BLOCH, ROBERT G., *et al.*, 174

FRAY, W. W. See KALTREIDER, NOLAN L., *et al.*, 662

Functional test in chronic pulmonary disease, 369

Generalized nodular tuberculosis, 354

GLICKMAN, L. GRANT. See SCHLOMOVITZ, BENJAMIN H., *et al.*, 369

Group examinations, Roentgenological, for pulmonary tuberculosis, 174

GUHA THAKURTHA, S. R., AND UKIL, A. C. The influence of sunlight upon experimental tuberculosis, 448

Gums and cheeks, Tuberculosis of the, 381

Haemorrhage in pulmonary tuberculosis, 88

HAMMOND, ARTHUR E. See WARREN, WADSWORTH, *et al.*, 315

HARPER, FRED R. A study of the results of treatment of pulmonary tuberculosis in Mexican and white patients, 556

KALTREIDER, NOLAN L., FRAY, W. W., AND HYDE, H. VAN ZILE. The effect of age on the total pulmonary capacity and its subdivisions, 662
KAMPMEIER, R. H. Tuberculous mediastinitis, 71
Kingston, Jamaica, Tuberculous infection in, 625
KLEIN, R. I., AND LEVINSON, S. A. The Weltmann serum coagulation reaction, 200
KOEPF, SHELDON W., AND MARTIN, GEORGE G. Tuberculosis of the gums and cheeks, 381
KOROL, EPHRAIM. Hernia of the lung, 39
KOZIELEK, VINCENT. See SWEANY, HENRY C., *et al.*, 484

Landis, Henry Robert Murray, 1872–1937, in memoriam, 100
LEGER, LEE H., AND WELKER, J. E. Generalized nodular tuberculosis, 354
Lesions, calcified intrathoracic, Intracutaneous tuberculin reaction associated with, 311
LEVINSON, S. A., AND KLEIN, R. I. The Weltmann serum coagulation reaction, 200
Lung, Hernia of the, 39
—— mobilization, Selective thoracoplasty with, 152
Lymph nodes, cervical, Tuberculosis of, 410

MARTIN, GEORGE G., AND KOEPF, SHELDON W. Tuberculosis of the gums and cheeks, 381
MARTINSEN, WILLIAM L. M., AND SWEANY, HENRY C. The incidence of extrapulmonary primary tuberculosis, 465
MASON, ELWOOD W. See BLOCH, ROBERT G., *et al.*, 174
MCCARTHY, CHARLES K. Haemorrhage in pulmonary tuberculosis, 88
Mediastinitis, Tuberculous, 71
Method, Flotation, of sputum examination, 525
Methods, diagnostic, roentgenological, Notes on the choice of, 1
Mexican and white patients, treatment of pulmonary tuberculosis in, Study of the results of, 556
MITCHELL, A. GRAEME. See NELSON, WALDO E., *et al.*, 286, 311
Mobilization, lung, Selective thoracoplasty with, 152
MOROZOVA, E. N. See WEISSFEILER, J., *et al.*, 93
Mortality, tuberculosis, in the United States, Sex differences in, 435

Negro colleges, Tuberculous infection in, 549
NELSON, WALDO E., MITCHELL, A. GRAEME, AND BROWN, ESTELLE W. The intracutaneous tuberculin reaction associated with calcified intrathoracic lesions, 311
——, —— ——., ——, ——. ——, —— ——, —— ——. The possibility of sensitization to tuberculin, 286
New cases, Degree of tuberculosis in, 57
Nodular tuberculosis, Generalized, 354
Noncaseating tuberculosis, 690
Notes on the choice of roentgenological diagnostic methods, 1

Oleothorax, Experimental, 245
O'NEILL, DALLETT B. See WEYL, CHARLES, *et al.*, 1
OVERHOLT, RICHARD H. Selective thoracoplasty with lung mobilization, 152

Patients in tuberculosis hospitals, Psychotherapy of rehabilitation of, 61
——, Mexican and white, treatment of pulmonary tuberculosis in, Study of the results of, 556
Phrenic-nerve interruption, Bilateral, in the treatment of pulmonary tuberculosis, 420
Physical examinations, fluoroscopic, roentgenographic and, Relative value of, in a tuberculosis case-finding program in university students, 49
PINNER, MAX. Noncaseating tuberculosis, 690
PLUNKETT, ROBERT E. Tuberculosis control, 612
Pneumococcus infection, experimental, in tuberculous rabbits, Course of, 93
Pneumothorax, therapeutic, Tuberculous dissemination during, 494
—— therapy, Positive intrapleural pressure as an aid to, 542
—— treatment, Fluoroscopy during, 634

## ERRATUM

VOLUME XXXVII, JANUARY–JUNE, 1938

An omission in the Index of Subjects and Authors, made at the time of paging the index, has just been discovered. The entries below should be inserted following page 731.


Has tuberculosis treatment been effective? (editorial), 254

Hernia of the lung, 39

HINCKS, CLARENCE M. The psychotherapy of rehabilitation of patients in tuberculosis hospitals, 61

HIRSCHBERG, NELL, AND ARNOLD, LLOYD. The effect of human tissue juices on tubercle bacilli, 598

Hospitals, tuberculosis, Psychotherapy of rehabilitation of patients in, 61

HOWE, JOHN S. Daily variations in the tuberculin reaction.

1. The range of variation in tuberculous and control subjects, 264
2. Relation to the vascular pressor episode, 273

Human tissue juices, Effect of, on tubercle bacilli, 598

HYDE, H. VAN ZILE. See KALTREIDER, NOLAN L., *et al.*, 662

Immunity tests, Statistical basis of errors in, 259

Incidence of extrapulmonary primary tuberculosis, 465

Infection, pneumococcus, experimental, in tuberculous rabbits, Course of, 93

——, Tuberculous, in Kingston, Jamaica, 625

——, ——, in Negro colleges, 549

Influence of sunlight upon experimental tuberculosis, 448

Intracutaneous reactions against antiserum in tuberculosis, 238

—— tuberculin reaction associated with calcified intrathoracic lesions, 311

Intrapleural fibrin bodies, 81

—— pressure, Positive, as an aid to pneumothorax therapy, 542

Intrathoracic lesions, calcified, Intracutaneous tuberculin reaction associated with, 311

Jamaica, Kingston, Tuberculous infection in, 625

——, Tuberculosis survey in, 560

Joints, bones and, tuberculosis in, Roentgenographic features of, 31

JORESS, MARK H., AND ROBINS, SAMUEL A. Intrapleural fibrin bodies, 81

Positive intrapleural pressure as an aid to pneumothorax therapy, 542
Possibility of sensitization to tuberculin, 286
POTTENGER, F. M. The clinical versus the Public Health point of view in the treatment of tuberculosis, 533
POU, JAIME F., AND CHARR, ROBERT. Thrombosis of pulmonary artery, 394
Present trend of case fatality rates in tuberculosis, 125
Pressure, intrapleural, Positive, as an aid to pneumothorax therpy, 542
Primary complex, Progressive, 346
—— tuberculosis, extrapulmonary, Incidence of, 465
Prognosis of the cavity bearer, 65
Program, tuberculosis case-finding, in university students, Relative value of fluoroscopic, roentgenographic and physical examinations in a, 49
Progressive primary complex, 346
Psychotherapy of rehabilitation of patients in tuberculosis hospitals, 61
Public Health point of view, Clinical versus the, in the treatment of tuberculosis, 533
Pulmonary artery, Thrombosis of, 394
—— capacity, total, and its subdivisions, Effect of age on the, 662
—— disease, chronic, Functional test in, 369
—— tuberculosis, Haemorrhage in, 88
—— —— in Mexican and white patients, treatment of, Study of the results of, 556
—— ——, Roentgenological group examinations for, 174
—— ——, treatment of, Bilateral phrenic-nerve interruption in the, 420

Rabbits, Tuberculous bacillaemia in,
1. Bacillaemia in nonallergic animals, 507
2. Bacillaemia in allergic animals, 520
——, ——, Course of experimental pneumococcus infection in, 93
Reaction, tuberculin, Daily variations in the,
1. The range of variation in tuberculous and control subjects, 264
2. Relation to the vascular pressor episode, 273
——, ——, Intracutaneous, associated with calcified intrathoracic lesions, 311
——, Weltmann serum coagulation, 200
Reactions, Intracutaneous, against antiserum in tuberculosis, 238
Rehabilitation of patients in tuberculosis hospitals, Psychotherapy of, 61
Relative value of fluoroscopic, roentgenographic and physical examinations in a tuberculosis case-finding program in university students, 49
REST, ARTHUR, AND SCHWATT, HERMAN. Prognosis of the cavity bearer, 65
Results of treatment of pulmonary tuberculosis in Mexican and white patients, Study of the, 556
Retrogressive changes of tubercles, Studies on the, 484
ROBINS, SAMUEL A., AND JORESS, MARK H. Intrapleural fibrin bodies, 81
Roentgenographic features of tuberculosis in bones and joints, 31
——, fluoroscopic, and physical examinations, Relative value of, in a tuberculosis case-finding program in university students, 49
Roentgenography, chest, Auxiliary techniques in, 14
Roentgenological diagnostic methods, Notes on the choice of, 1
—— group examinations for pulmonary tuberculosis, 174

SALEY, D. H., WILLIS, H. S., AND ELLWART, LUCIA. Experimental oleothorax, 245
SCHLOMOVITZ, BENJAMIN H., THOMPSON, A. B., AND GLICKMAN, L. GRANT. A functional test in chronic pulmonary disease, 369
SCHWATT, HERMAN, AND REST, ARTHUR. Prognosis of the cavity bearer, 65
Selective thoracoplasty with lung mobilization, 152
Sensitization to tuberculin, Possibility of, 286
Serum coagulation reaction, Weltmann, 200
Sex differences in tuberculosis mortality in the United States, 435
SHEPARD, CHARLES E. See BOYNTON, RUTH E., *et al.*, 49
SHIPMAN, SIDNEY J. Bronchial factor in cavitation, 336
SMITH, C. RICHARD. The flotation method of sputum examination, 525

SMITH, H. H., AND WELLS, C. W. Tuberculous infection in Kingston, Jamaica, 625
Sputum examination, Flotation method of, 525
Statistical basis of errors in immunity tests, 259
STRUKOV, A. I. See WEISSFEILER, J., *et al.*, 93
Students, university, tuberculosis case-finding program in, Relative value of fluoroscopic, roentgenographic and physical examinations in a, 49
Studies in avian tuberculosis.
1. Avian tubercle bacilli in generalized disease in swine, 579
2. Comparative virulence of avian and bovine tubercle bacilli for rabbits and guinea pigs, 582
3. Sensitization method of differentiating avian from bovine infection in guinea pigs and rabbits, 588
4. The possible rôle of the avian tubercle bacillus in infection in man, 594

—— on the retrogressive changes of tubercles, 484
Study of the results of treatment of pulmonary tuberculosis in Mexican and white patients, 556
Sunlight, Influence of, upon experimental tuberculosis, 448
Survey, Tuberculosis, in Jamaica, 560
SUTHERLAND, CHARLES G., AND ADDINGTON, ERCELL A. Roentgenographic features of tuberculosis in bones and joints, 31
SWEANY, HENRY C., AND MARTINSEN, WILLIAM L. M. The incidence of extrapulmonary primary tuberculosis, 465
——, —— ——., TILLOTSON, ALMA E., AND KOZIELEK, VINCENT. Studies on the retrogressive changes of tubercles, 484

Techniques, Auxiliary, in chest roentgenography, 14
TELFORD, P. K. The degree of tuberculosis in new cases, 57
Test, Functional, in chronic pulmonary disease, 369
Tests, immunity, Statistical basis of errors in, 259
Therapeutic pneumothorax, Tuberculous dissemination during, 494
Therapy, pneumothorax, Positive intrapleural pressure as an aid to, 542
THOMPSON, A. B. See SCHLOMOVITZ, BENJAMIN H., *et al.*, 369
THOMPSON, BRIAN C. Tuberculosis of cervical lymph nodes, 410
Thoracoplasty, Selective, with lung mobilization, 152
Thrombosis of pulmonary artery, 394
TILLOTSON, ALMA E. See SWEANY, HENRY C., *et al.*, 484
Tissue juices, human, Effect of, on tubercle bacilli, 598
Total pulmonary capacity and its subdivisions, Effect of age on the, 662
Tracheobronchitis, tuberculous, Diagnosis and treatment of, 315
Treatment of pulmonary tuberculosis, Bilateral phrenic-nerve interruption in the, 420
—— —— —— —— in Mexican and white patients, Study of the results of, 556
—— —— tuberculosis, Clinical versus the Public Health point of view in the, 533
—— —— tuberculous tracheobronchitis, Diagnosis and, 315
——, pneumothorax, Fluoroscopy during, 634
——, tuberculosis, been effective, Has, (editorial), 254
Tubercle bacilli, Effect of human tissue juices on, 598
Tubercles, retrogressive changes of, Studies on the, 484
Tuberculin reaction, Daily variations in the,
1. The range of variation in tuberculous and control subjects, 264
2. Relation to the vascular pressor episode, 273

—— ——, Intracutaneous, associated with calcified intrathoracic lesions, 311
——, sensitization to, Possibility of, 286
Tuberculosis, avian, Studies in,
1. Avian tubercle bacilli in generalized disease in swine, 579
2. Comparative virulence of avian and bovine tubercle bacilli for rabbits and guinea pigs, 582
3. Sensitization method of differentiating avian from bovine infection in guinea pigs and rabbits, 588

4. The possible rôle of the avian tubercle bacillus in infection in man, 594
Tuberculosis, case fatality rates in, Present trend of, 125
—— case-finding program in university students, Relative value of fluoroscopic, roentgenographic and physical examinations in a, 49
—— control, 612
——, Degree of, in new cases, 57
——, experimental, Influence of sunlight upon, 448
—— hospitals, Psychotherapy of rehabilitation of patients in, 61
—— in bones and joints, Roentgenographic features of, 31
——, Intracutaneous reactions against antiserum in, 238
—— mortality in the United States, Sex differences in, 435
——, nodular, Generalized, 354
——, Noncaseating, 690
—— of cervical lymph nodes, 410
—— —— the gums and cheeks, 381
——, primary, extrapulmonary, Incidence of, 465
——, pulmonary, Haemorrhage in, 88
——, ——, in Mexican and white patients, treatment of, Study of the results of, 556
——, ——, Roentgenological group examinations for, 174
——, ——, treatment of, Bilateral phrenic-nerve interruption in the, 420
—— survey in Jamaica, 560
—— treatment been effective, Has, (editorial), 254
——, —— of, Clinical versus the Public Health point of view in the, 533
Tuberculous bacillaemia in rabbits.
1. Bacillaemia in nonallergic animals, 507
2. Bacillaemia in allergic animals, 520
—— dissemination during therapeutic pneumothorax, 494
—— infection in Kingston, Jamaica, 625
—— —— —— Negro colleges, 549
—— mediastinitis, 71
—— rabbits, Course of experimental pneumococcus infection in, 93
—— tracheobronchitis, Diagnosis and treatment of, 315
Tuttle, William M. See Warren, Wadsworth, *et al.*, 315

Ukil, A. C., and Guha Thakurtha, S. R. The influence of sunlight upon experimental tuberculosis, 448
United States, Sex differences in tuberculosis mortality in the, 435
University students, tuberculosis case-finding program in, Relative value of fluoroscopic, roentgenographic and physical examinations in a, 49

Variations in the tuberculin reaction, Daily,
1. The range of variation in tuberculous and control subjects, 264
2. Relation to the vascular pressor episode, 273
Vidal, C. B., and Corper, H. J. Intracutaneous reactions against antiserum in tuberculosis, 238

Warren, S. Reid, Jr. See Weyl, Charles, *et al.*, 1
Warren, Wadsworth, Hammond, Arthur E., and Tuttle, William M. The diagnosis and treatment of tuberculous tracheobronchitis, 315
Weissfeiler, J., Morozova, E. N., and Strukov, A. I. The course of experimental pneumococcus infection in tuberculous rabbits, 93
Welker, J. E., and Leger, Lee H. Generalized nodular tuberculosis, 354
Wells, C. W., and Smith, H. H. Tuberculous infection in Kingston, Jamaica, 625
Weltmann serum coagulation reaction, 200
Weyl, Charles, Warren, S. Reid, Jr., and O'Neill, Dallett B. Notes on the choice of roentgenological diagnostic methods, 1
White patients, Mexican and, treatment of pulmonary tuberculosis in, Study of the results of, 556
Willauer, George, and Cohen, Robert V. Bilateral phrenic-nerve interruption in the treatment of pulmonary tuberculosis, 420
Willis, H. S. See Saley, D. H., *et al.*, 245

Zavod, William A. Tuberculous dissemination during therapeutic pneumothorax, 494
Zintheo, Clarence J., Jr. Auxiliary techniques in chest roentgenography, 14